DOCKET NO. 01P-0471/CP-1

SUPPORTING DOCUMENTS FOR PETITION RESPONSE

TAB E: 50 FR 51002 (December 13, 1985)

TAB F: Current Labeling of Anthrax Vaccine Adsorbed (Biothrax)

TAB G: Prior Labeling of Anthrax Vaccine, Adsorbed (Package Insert)

TAB H: Berlex Laboratories, Inc. v. Food and Drug Administration, 942 F. Supp. 19 (D.D.C. 1966)

TAB I: 65 FR 31003 (May 15, 2000)

TAB J: 52 FR 11123 (April 4, 1987)

TAB K: 61 FR 40153 (August 1, 1996)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

21 CFR PART 610

[DOCKET NO. 80N-0208]

50FR 51002
12-13-85

BIOLOGICAL PRODUCTS; BACTERIAL VACCINES AND TOXOIDS;
IMPLEMENTATION OF EFFICACY REVIEW

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing
to amend the biologics regulations in response to the report
and recommendations of the Panel on Review of Bacterial Vaccines
and Toxoids (the Panel). The Panel reviewed the safety, efficacy,
and labeling of bacterial vaccines and toxoids with standards of
potency, antitoxins, and immune globulins. On the basis of the
Panel's findings and recommendations, FDA is proposing to
classify these products in Category I (safe, effective, and
not misbranded), Category II (unsafe, ineffective, or misbranded),
or Category IIIB (off the market pending completion of studies
permitting a determination of effectiveness). Products recommended
for Category IIIA (formerly defined as on the market during
further studies in support of effectiveness) will be reviewed
by the Vaccines and Related Biological Products Advisory Committee

80-319

NPR 1

for reclassification into Category I or II. In the near future, FDA will publish a notice of opportunity for hearing (NOH) to revoke the licenses for products in Category II and Category IIIB. Comments and additional data will be requested in the NOH.

DATES: Comments on the proposed classification of products into Category I and on proposed amendments to the biologics regulations should be submitted by (insert date 90 days after date of publication in the FEDERAL REGISTER). Comments on the confidentiality of data submitted for review by the Panel should be submitted before (insert date 30 days after date of publication in the FEDERAL REGISTER). FDA proposes that any final regulation based on this proposal become effective 60 days after the date the final regulation is published in the FEDERAL REGISTER. Labeling requirements, including the requirements in §§ 201.56 and 201.57 (21 CFR 201.56 and 201.57), would become effective 30 months after the date of publication of the final rule in the FEDERAL REGISTER.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Steven F. Falter,

Center for Drugs and Biologics (HFN-364),

Food and Drug Administration,

5600 Fishers Lane,

Rockville, MD 20857,

301-443-3650.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of
February 13, 1973 (38 FR 4319), FDA issued § 601.25 (21 CFR
601.25) concerning procedures for the review of the safety,
effectiveness, and labeling of biological products licensed
prior to July 1, 1972. Under the panel assignments published
in the FEDERAL REGISTER of June 19, 1974 (39 FR 21176), the
biological products reviewed were assigned to one of the
following categories: (a) bacterial vaccines and bacterial
antigens with "no U.S. standard of potency," (b) bacterial
vaccines and toxoids with standards of potency, (c) viral
vaccines and rickettsial vaccines, (d) allergenic extracts,
(e) skin test antigens, and (f) blood and blood derivatives.

Under § 601.25, FDA assigned responsibility for the initial
review of each of the biological product categories to a separate
independent advisory panel consisting of qualified experts to
ensure objectivity of the review and public confidence in the
use of these products. Each panel was charged with preparing an
advisory report to the Commissioner which was to: (1) evaluate
the safety and effectiveness of the biological products, (2)
review labeling of the biological products, and (3) identify
the biological products under review that are safe, effective,
and not misbranded. The advisory report includes recommendations
classifying products into one of three categories.

Category I designates those biological products determined by the Panel to be safe, effective, and not misbranded. The Panel's statement may include any condition relating to active components, labeling, tests required prior to release of batches, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

Category II designates those biological products determined by the Panel to be unsafe, ineffective, or misbranded.

Category III designates those biological products determined by the Panel not to fall within either Category I or II on the basis of the Panel's conclusion that the available data are insufficient to classify such biological products, and for which further testing is therefore required. Those biological products in Category III for which continued licensing, manufacturing, and marketing during the period of further testing are recommended are designated as Category IIIA. Those biological products in Category III for which suspension of the product licenses pending submission of additional data are recommended are designated as Category IIIB. The recommendation for either Category IIIA or IIIB is based on assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time, while questions raised concerning the products are being resolved by further study.

The definition above of Category IIIA was applied at the time of the Panel's review and served as a basis for the Panel's recommendations. In the FEDERAL REGISTER of October 5, 1982 (47 FR 44062), FDA revised § 601.25 and created a new § 601.26 (21 CFR 601.26) to provide for the review by an advisory review panel of products currently recommended to be in Category IIIA. The purpose of the review will be to reclassify each Category IIIA product into either Category I or Category II as defined above, based on the available evidence for effectiveness. A more detailed description of the procedures for the review and reclassification of the products recommended for Category IIIA by the Panel appears later in this document in paragraph 1d of FDA's response to the Panel's report.

In this advisory report, some biological products are designated as Category IIIC, based on the Panel's conclusion that it was not possible to classify these products because of essentially administrative problems, rather than because of scientific questions. For example, some licenses are held for products which the manufacturer has not produced or marketed for many years. Other licenses are held for products for which there is no labeling, and which are manufactured only for combination with other biologically active components. The Panel has recommended that the licenses for products placed in Category IIIC be revoked, because the Panel was unable to

determine the potential benefits and risks of the products in the event they were to be marketed. However, the Panel noted that in some cases it may be preferable for FDA and the manufacturer to take appropriate administrative actions to satisfactorily resolve information deficiencies, rather than to revoke the product license.

In the FEDERAL REGISTER of February 28, 1973 (38 FR 4359), FDA requested data and information regarding bacterial vaccines and toxoids with U.S. standards of potency. Additional data and information regarding the safety and effectiveness of related immune globulins and sera were requested in the FEDERAL REGISTER of June 19, 1974 (38 FR 21176).

Some concern has been expressed that information submitted to FDA under § 601.25 will become public information. Data and information submitted in response to the February 28, 1973 and June 19, 1974 notices and falling within the provisions of 5 U.S.C. 552(b), 18 U.S.C. 1905, or 21 U.S.C. 331(j) have been handled as confidential. However, with the publication of this proposed implementation and the Panel's findings, such data and information will, under § 601.25(b)(2), be made publicly available after (insert date 30 days after the date of publication in the FEDERAL REGISTER), and may be reviewed at the office of the Dockets Management Branch, except to the extent that the person submitting the data and information demonstrates that it still falls within the confidentiality provisions of one or more of

the above statutes. Accordingly, comments concerning confiden-
tiality should be submitted by (insert date 30 days after the
date of publication in the FEDERAL REGISTER). A letter dated
Oct 21/85, was sent to each manufacturer having products under
review by this Panel, informing them of the impending release of
data and information and asking that the manufacturers promptly
submit any comments concerning confidentiality.

The Panel appointed by FDA to review the data and information
submitted and to prepare a report on the safety, effectiveness,
and labeling of bacterial vaccines, toxoids, related antitoxins,
and immune globulins included the following individuals:

Panel Chairman, Gene H. Stollerman,

M.D., Professor and Chairman, Department

of Medicine, University of Tennessee College

Memphis, TN 38163 (now Professor of Medicine,

Boston University Medical Center);

Geoffery Edsall, M.D. (deceased), Professor

Emeritus of Microbiology (Harvard School of

Public Health and London School of Hygiene

and Tropical Medicine);

Theodore C. Eickhoff, M.D., Professor

of Medicine, Head, Division of Infectious

Diseases, University of Colorado Medical

Center, Denver, CO 80262;

John C. Feeley, Ph.D., Chief, Bacterial
Immunology Branch (now Assistant Director
for Laboratory Sciences, Bacterial Disease
Division), Centers for Disease Control, Atlanta,
GA 30333;

Hjordis M. Foy, M.D., Ph.D. Associate
Professor (Since July 1, 1976, Professor),
Department of Epidemiology, School of Public
Health and Community Medicine, University
of Washington, Seattle, WA 98195;

Edward A. Mortimer, Jr., M.D., Chairman of
the Department of Pediatrics, School of Medicine,
University of New Mexico, Albuquerque, NM 87131.
(Since February 1, 1975, Professor and Chairman
of the Department of Community Health and Professor
of Pediatrics, School of Medicine, Case Western
Reserve University, Cleveland, OH 44106.)

Jay P. Sanford, M.D., Professor,
Department of Internal Medicine, University
of Texas, Southwestern Medical School at Dallas,
Dallas, TX 75235. (Since June 1, 1975, Dean,
School of Medicine, Uniformed Services University,
Bethesda, MD 20014.)

The Panel was convened on July 12, 1973, in an organizational meeting. Working meetings were held on: July 12, September 24-25, November 9-10, December 13-14, 1973; February 13-14, April 9-10, June 13-14, September 12-13, November 7-8, 1974; January 13-14, February 24-25, May 15-16, June 19-20, September 11-12, November 20-21, 1975; January 12-13, March 27-28, May 17-18, July 22-23, October 23, December 14-15, 1976; March 24-25, December 12-13, 1977; and February 1-2, 1979.

Two nonvoting liaison representatives served on the Panel. Ms. Laryl Lee Delker, nominated by the Consumer Federation of America, served as the consumer representative. John Adams, Ph.D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Karl Bambach, Ph.D., substituted for Dr. Adams during his absences. Morris Schaeffer, M.D., Ph.D., participated in the Panel meetings in his capacity as Director of the Office of Scientific Advisors and Consultants, FDA. Jack Gertzog, Deputy Director, Office of Scientific Advisors and Consultants, FDA, served as Executive Secretary of the Panel. Margaret Pittman, Ph.D., was selected by the Panel as a consultant.

Over 120 persons requested an opportunity or were other-wise invited to appear before the Panel and present their views on one or more of the vaccines and related matters. Every person who requested an opportunity was heard by the Panel. The names of these persons are on file with the Dockets Management Branch.

The Panel on Review of Bacterial Vaccines and Toxoids evaluated all data submitted for the following vaccines, toxoids, and other related products:

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL

Manufacturer	Product
Abbott Laboratories.	Tetanus Immune Globulin (Human).
Advance Biofacturers Corp.	Collagenase.
Armour Pharmaceutical Co.	Tetanus Immune Golbulin (Human).
Bureau of Laboratories, Michigan Department of Public Health.	Anthrax Vaccine Adsorbed, Diphtheria Antitoxin, Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Diphtheria Toxoid Adsorbed, Pertussis Vaccine,

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--Con.

Manufacturer	Product
	Pertussis Vaccine Adsorbed,
	Tetanus Immune Globulin (Human),
	Tetanus Toxoid Adsorbed,
	Typhoid Vaccine.
Connaught Laboratories, Ltd.	BCG Vaccine,
	Botulism Antitoxin,
	Diphtheria Toxoid,
	Tetanus Toxoid.
Cutter Laboratories, Inc.	Pertussis Immune Globulin (Human),
	Plague Vaccine,
	Tetanus Immune Globulin (Human),
	Tetanus Toxoid.
Dow Chemical Co. (The).	Diphtheria and Tetanus Toxoids Adsorbed,
	Diphtheria Tetanus Toxoids and Pertussis Vaccine Adsorbed,
	Diphtheria Toxoid,

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--Con.

Manufacturer	Product
	Diphtheria Toxoid and Pertussis Vaccine Adsorbed,
	Pertussis Vaccine,
	Tetanus Immune Globulin (Human),
	Tetanus Toxoid,
	Tetanus Toxoid, Adsorbed.
Eli Lilly and Co.	Cholera Vaccine,
	Diphtheria and Tetanus Toxoids,
	Diphtheria and Tetanus Toxoids Adsorbed,
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed,
	Pertussis Vaccine,
	Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use),
	Tetanus Toxoid,

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--Con.

Manufacturer	Product
	Tetanus Toxoid Adsorbed,
	Typhoid Vaccine.
E. R. Squibb and Sons, Inc.	Tetanus Immune Globulin
	(Human).
Glaxo Laboratories, Ltd.	BCG Vaccine.
Istituto Sieroterapico	Diphtheria Antitoxin,
Vaccinogeno Toscano "Sclavo".	Diphtheria Toxoid,
	Diphtheria Toxoid
	Adsorbed,
	Tetanus Antitoxin,
	Tetanus Toxoid,
	Tetanus Toxoid Adsorbed.
Lederle Laboratories,	Botulism Antitoxin,
Division American	Cholera Vaccine,
Cyanamid Co.	Diphtheria Antitoxin,
	Diphtheria and Tetanus
	Toxoids Adsorbed,
	Diphtheria and Tetanus
	Toxoids and Pertussis
	Vaccine Adsorbed,

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--Con.

Manufacturer	Product
	Gas Gangrene Polyvalent Antitoxin,
	Pertussis Vaccine,
	Streptokinase-Streptodornase,
	Tetanus Antitoxin,
	Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use),
	Tetanus and Gas Gangrene Polyvalent Antitoxin,
	Tetanus Immune Globulin (Human),
	Tetanus Toxoid,
	Tetanus Toxoid Adsorbed.
Massachusetts Public Health Biologic Laboratories.	Diphtheria Antitoxin,
	Diphtheria and Tetanus Toxoids Adsorbed,
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed,
	Diphtheria Toxoid,
	Tetanus Antitoxin,
	Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use),

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--Con.

Manufacturer	Product
	Tetanus Immune Globulin (Human),
	Tetanus Toxoid,
	Tetanus Toxoid Adsorbed,
	Typhoid Vaccine.
Merck Sharp & Dohme, Division of Merck & Co., Inc.	Cholera Vaccine,
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed,
	Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use),
	Tetanus Toxoid,
	Tetanus Toxoid Adsorbed,
	Tetanus Immune Globulin (Human),
	Typhoid Vaccine.
Merrell-National Laboratories, Division of Richarson-Merrell, Inc.	Cholera Vaccine,
	Diphtheria Antitoxin,
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine,

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--Con.

Manufacturer	Product
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed,
	Diphtheria Toxoid,
	Pertussis Vaccine,
	Tetanus Antitoxin,
	Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use),
	Tetanus Toxoid,
	Tetanus Toxoid Adsorbed.
Metabolic, Inc.	Tetanus Immune Globulin (Human).
Osterreichisches Institut Fur Haemoderivate G.m.b.H.	Tetanus Immune Globulin (Human).
Parke, Davis and Co.	Diphtheria and Tetanus Toxoids,
	Diphtheria and Tetanus Toxoids Adsorbed,
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Poliomyelitis Vaccine,
	Diphtheria and Tetanus Toxoids and Pertussis and Poliomyelitis Vaccines Adsorbed,

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--Con.

Manufacturer	Product
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine,
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed,
	Diphtheria Toxoid,
	Diphtheria Toxoid Adsorbed,
	Pertussis Vaccine,
	Pertussis Vaccine Adsorbed,
	Tetanus Antitoxin,
	Tetanus Immune Globulin (Human),
	Tetanus Toxoid,
	Tetanus Toxoid Adsorbed.
Swiss Serum and Vaccine Institute, Berne.	Tetanus Antitoxin, Tetanus Toxoid Adsorbed.
Texas Department of Health Resources.	Diphtheria and Tetanus Toxoids Adsorbed,
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed,

TABLE 1--LIST OF PRODUCTS REVIEWED BY PANEL--Con.

Manufacturer	Product
	Diphtheria Toxoid,
	Pertussis Vaccine,
	Tetanus and Diphtheria Toxoids Adsorbed (For Adult use),
	Tetanus toxoid,
	Typhoid Vaccine.
Travenol Laboratories, Inc., Hyland Division.	Pertussis Immune Globulin (Human),
	Tetanus Immune Globulin (Human).
University of Illinois.	BCG Vaccine.
Wyeth Laboratories, Inc.	Cholera Vaccine,
	Diphtheria and Tetanus Toxoids Adsorbed,
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed,
	Diphtheria Toxoid,
	Diphtheria Toxoid Adsorbed,
	Pertussis Vaccine,
	Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use),
	Tetanus Immune Globulin (Human),
	Tetanus Toxoid,
	Tetanus Toxoid Adsorbed,
	Typhoid Vaccine.

Only biological products that were licensed prior to July 1, 1972, are reviewed in this report.

The Advisory Panel appointed to review data and information concerning safety, effectiveness, and labeling of bacterial vaccines and toxoids has completed its review as follows:

BASIS OF EVALUATION

1. General background and history. The diseases of man caused by bacteria and by some of their specific extracellular toxins from which useful vaccines have been produced represent extraordinarily diverse pathologic processes. The diseases range from tetanus to tuberculosis; the former is an acute illness caused by a single well-defined toxin and the latter is a chronic disease due to intricate bacterial-host cell interactions resulting in a wide variety of lesions. Moreover, the degree of protection offered by current immunization practices against these diseases range from virtually complete efficacy, as in the case of tetanus, to a very limited and temporary benefit, as in the case of cholera. A brief account of the history of immunization against these diseases may help both the lay and professional public to appreciate the background of our current achievements and dilemmas against which this Panel has been obliged to exercise its judgment in assessing the safety and efficacy of the products under its purview.

It is important for the public and its agencies to
appreciate the tentative and evolving nature of the science
of immunization, particularly to combat the notion that decisions
made in the public interest at one point in time are necessarily
valid and binding at another. The foundations of the modern
science of bacteriology are no more than a century old and
were laid by Louis Pasteur and Robert Koch, who died within
the memory of some persons still alive. Pasteur not only
established the germ theory of disease, but, just 100 years
ago (in 1877) discovered and applied the principles of active
immunization by using living, attenuated cultures--"live
vaccines." He argued that if Jenner could use cowpox (what
Pasteur thought to be attenuated smallpox) as a vaccine, the
same might be done with attenuated anthrax. This he succeeded
in doing in preparing attenuated chicken cholera and anthrax
vaccines for animals. Subsequently, "killed" bacterial vaccines
were made by the end of the 19th century when A. E. Wright in
England, among others, began immunizing against typhoid fever
with heat-killed whole bacterial cells. Epidemics of cholera
and plague, rampant in various parts of the world at the time,
were quickly attacked with other vaccines many of which were
similarly made from killed whole bacteria. In all three
diseases, the vaccines seemed to afford some useful protection
before advances could be made in worldwide sanitation and well
before the introduction of antibiotics.

At the close of the 19th century, Koch was attempting to prevent and even to treat tuberculosis with tuberculin, the culture filtrate of tuburcule with bacilli. His failure to do so, plus the serious toxic and untoward effects that this treatment had on the disease, created reservations in the minds of both professionals and the public concerning the risks as well as the benefits of immunization attempts. Nonetheless, despite this setback, the first living bacterial vaccine to be used on a large scale in man came as a sequel to Koch's work when Calmette and Guerin introduced BCG vaccine into human immunization procedures in 1921.

To appreciate the speed of the development of the science of immunology, it is necessary to acknowledge not only the dramatic empirical discoveries of successful vaccines, but also the discovery of the immunologic processes upon which further progress in immunization was based. Two major forms of host defenses are referred to repeatedly in this report. They also have their origins in the medically tumultuous era of the late 19th century. Eli Metchnikoff, the Russion biologist who studied under Pasteur and eventually became a director of the Pasteur Institute, developed the concept of "phagocytosis." He gave the name of "phagocytes" (eating cells) to body cells in blood, blood vessels, lymph nodes, bone marrow, liver, and spleen which digest and destroy invading microorganisms as well as other foreign microparticles. This system of cellular immunity, responsible for the clearing of foreign

agents from within the host, he considered to be the backbone of host defense against infection. The "humoral theory" was introduced at the same time by G. H. F. Nutthall of Cambridge who studied the killing action of blood on bacteria (bactericidal effects). He showed these effects were due to chemical products of cells in blood serum and body fluids--substances called "antibodies" which could destroy or inactivate some bacteria without help from phagocytes. By 1894, Richard Pfeiffer, one of Koch's pupils, demonstrated that such antibodies caused the disintegration of cholera vibrios. These he called "bacteriolysins."

The synthesis of humoral and cellular mechanisms of immunity was proposed by Wright in 1903 when he demonstrated the pro-phagocytic effect of specific antibodies. Wright named antibodies "opsonins" or "bacteriotropins" which enhance the ability of phagocytic cells to recognize, ingest, and kill microorganisms. Although Wright's concepts of the interaction of antibodies and and cells applied well to antibacterial immunity against invasive bacterial diseases such as typhoid, pneumonia, streptococcal infections, and meningitis, it did not pertain as much to diseases produced by the action of toxins liberated by bacteria.

In diseases like diphtheria, tetanus, and botulism, neutralization of the soluble bacterial toxins (exotoxins) liberated during infection is of the utmost importance in the prevention of the diseases caused by these organisms. Thus, antibodies that neutralize such toxins are the basis of "antitoxic immunity," which constitutes an area of immunologic knowledge that is on a much firmer basis than the understanding of many forms of antibacterial immunity.
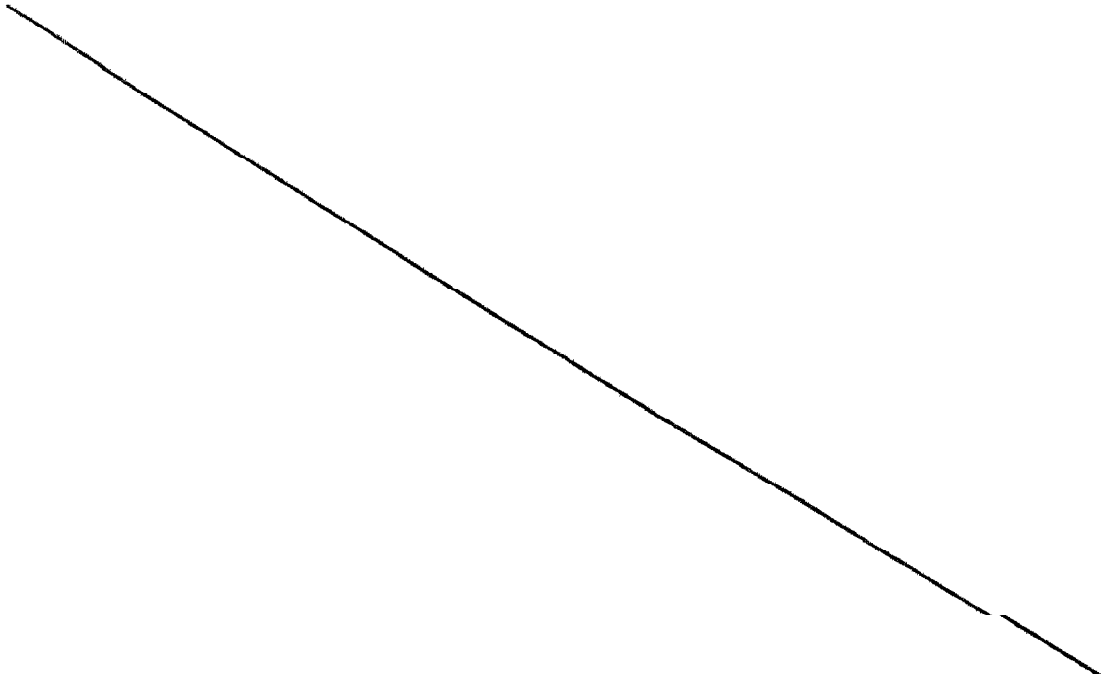
Again, in the last two decades of the 19th century, the
principles of antitoxic immunity were established when Pasteur's
associate, Pierre Roux, showed the diphtheria bacillus produced
a powerful soluble toxin in the culture filtrate of the organism.
Behring and Kitasato, disciples of Koch, by 1890 had prepared
an antibody to the diphtheria toxin which they termed "antitoxin"
and with such immune sera began the era of "passive immunization."
Thus, antitoxin (serum prepared in horses against such toxins)
could be used to prevent and treat certain diseases. The
denaturation of the toxins with the addition of formalin rendered
them harmless when injected into man and animals, but they still
retained their ability to produce antitoxin antibodies. "Active"
immunization against diphtheria and tetanus with these toxoids
subsequently became routine in most countries of the world.

"Passive" immunization consists of the injection of antibodies
made by another host, human or animal, into the person to be
protected. Antibodies remain in that person for only a short time,
however, until they are broken down, and thus provide only temporary
benefit. Active immunization, on the other hand, consists of
inducing the person to be protected to produce their own antibodies
by giving small doses of the microorganism or toxin in a form that
will not cause serious illness in the person. Once active immunity
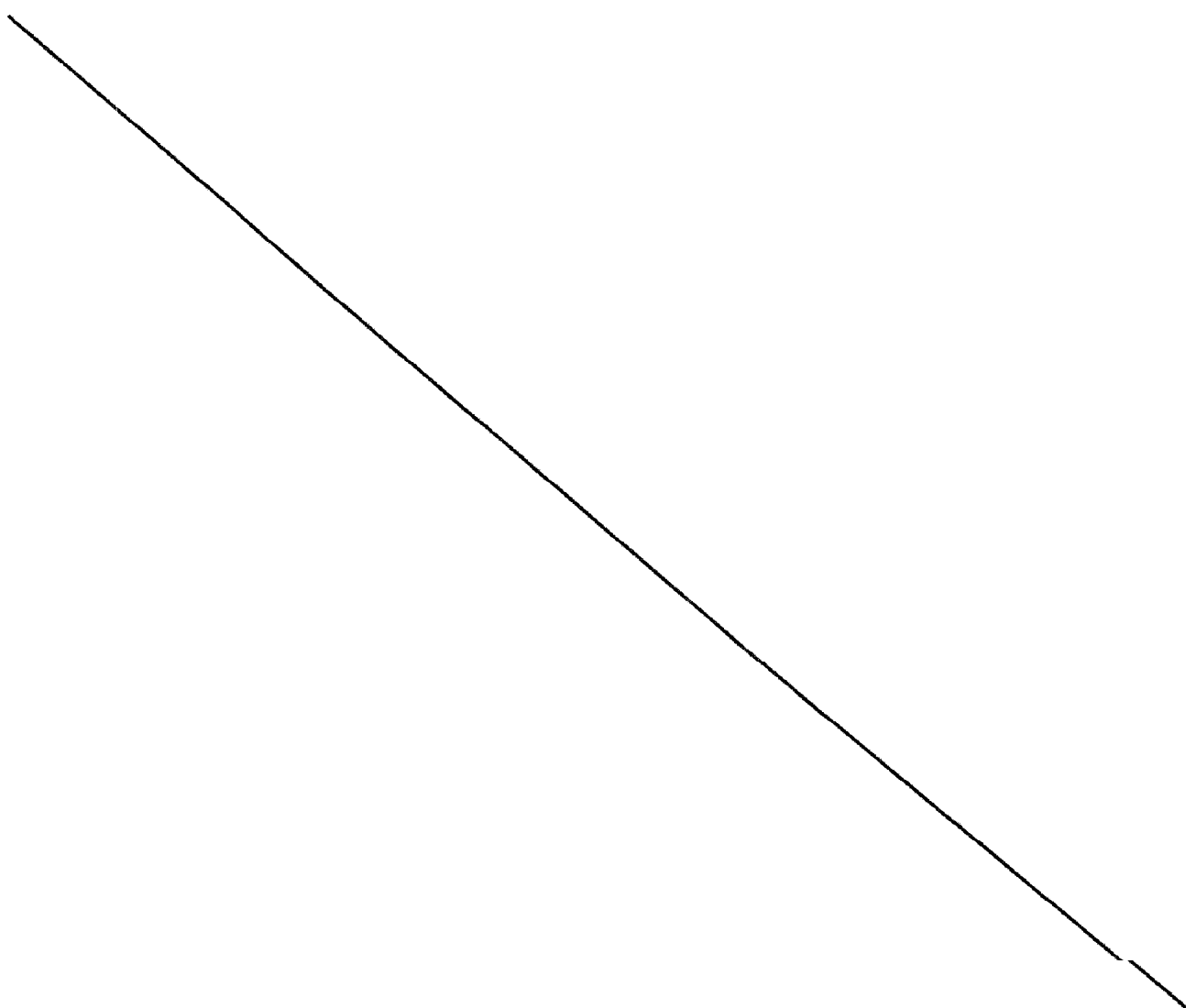is induced, it tends to persist for long periods of time.

The important differences between passive and active immunization were clearly established in the 1890's by Jules Bordet and by Paul Ehrlich whose brilliant career not only included the standardization of toxins and antitoxins and the foundations of modern immunochemistry, but also led to the recognition of the presence in the blood and body tissues of "complement," the system of enzymes that are activated by antigen-antibody complexes and that result in the cellular and vascular events of inflammation leading to the destruction of bacteria and viruses and to the stimulation of the host cells which phagocytize and destroy organisms.

From Ehrlich's systematic, quantitative approach to the neutralization of toxins emerged the triumph over diphtheria and subsequently, even more brilliantly, over tetanus. By the First World War, the lives of many wounded men were saved by passive tetanus immunization and the control of tetanus during the Second World War with the toxoid could be regarded as a modern miracle of immunization.
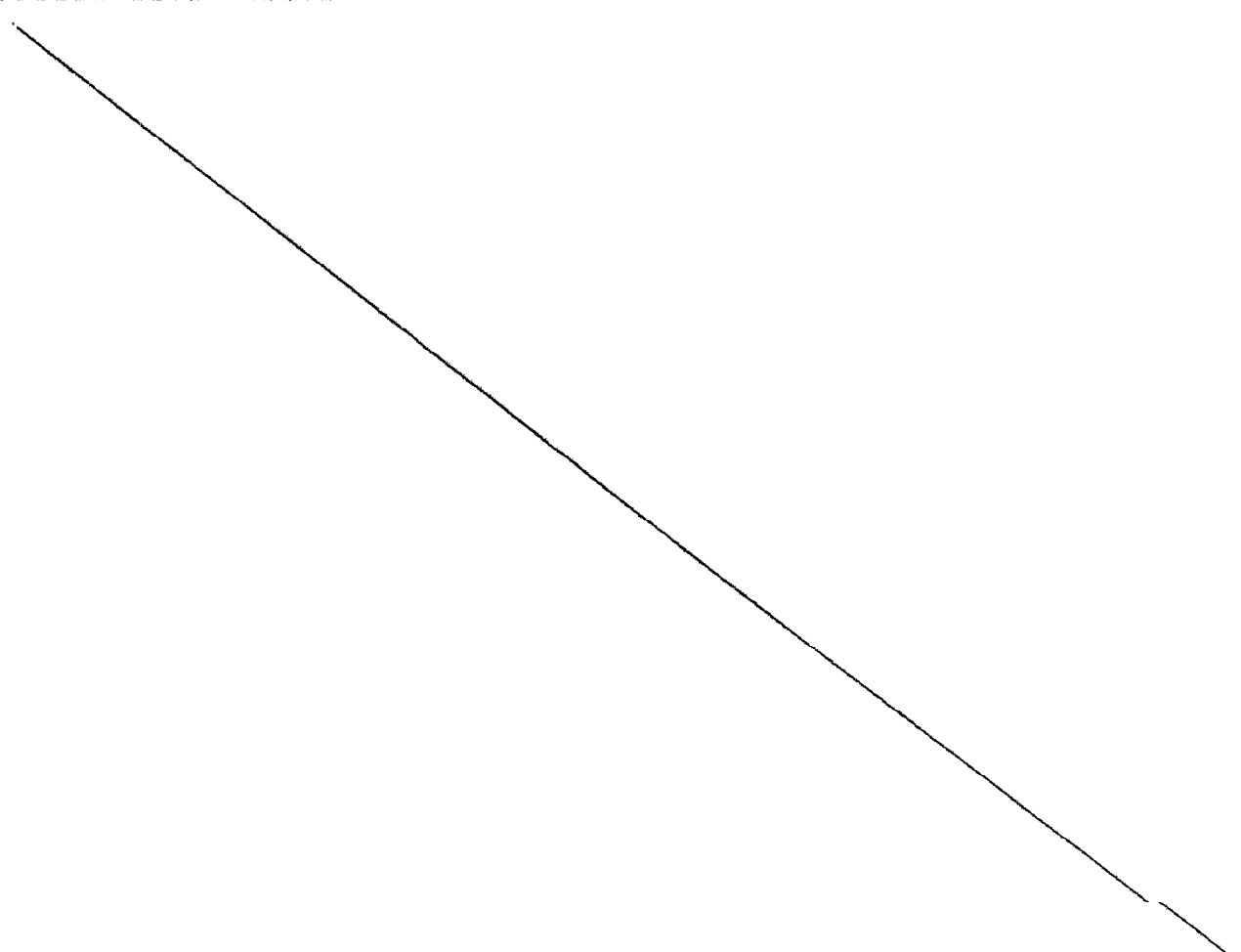
Soon after the beginnings of immunology came the development
of government supervising authorities in many countries to regulate
standards of purity and potency to which preparations had to conform
before they were released for public usage. The importance of
international standards of vaccines was recognized by the Health
Commission of the League of Nations which in 1929 appointed a
permanent Commission on Biological Standardization. As a result,
potency of vaccines were expressed in a more uniform notation which
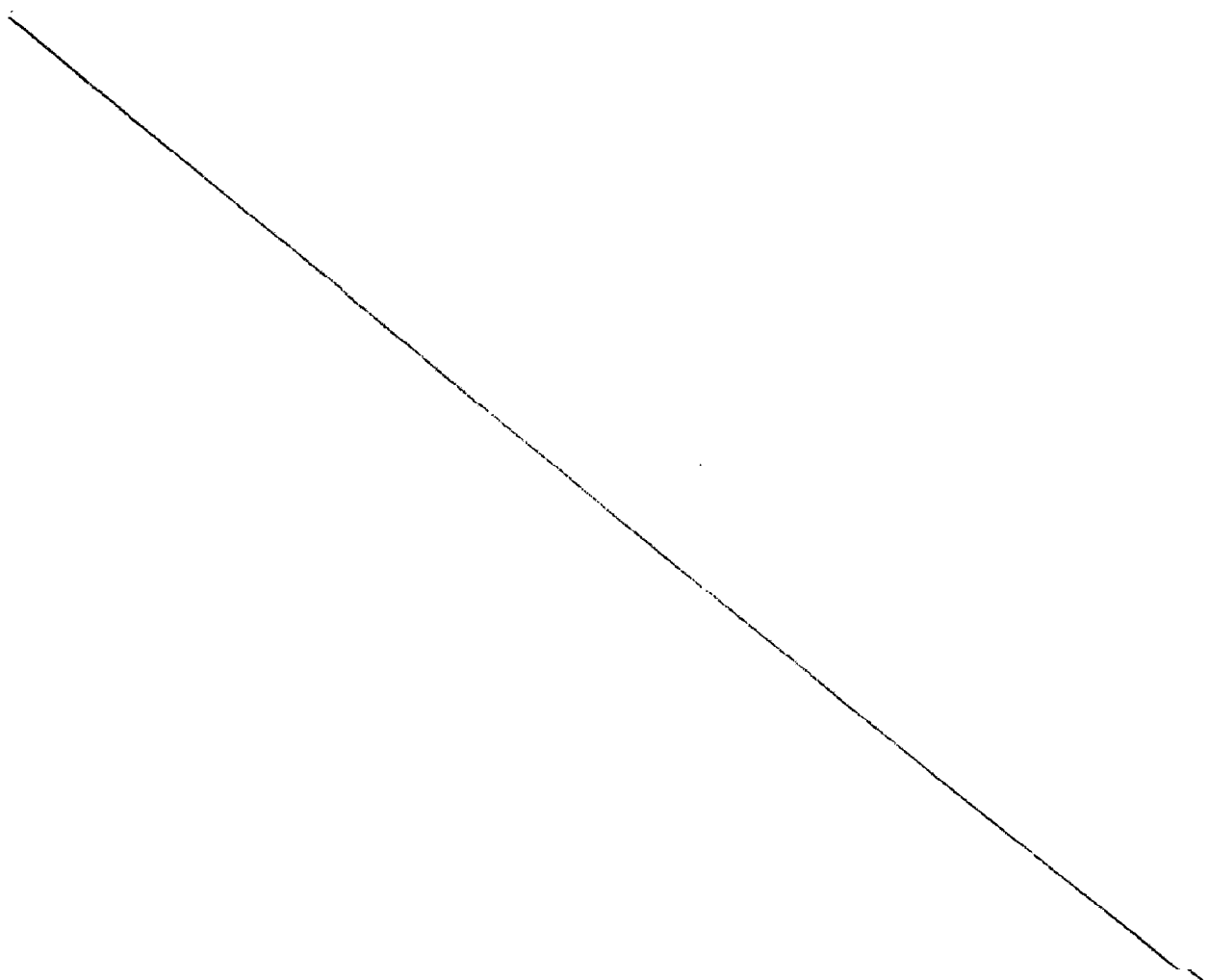was accepted and understood throughout the world.

In the United States and Great Britain, the control of biologic
substances for sale became essentially the responsibility of the
producing laboratory, but manufacturers worked under licenses issued
by government agencies such as the current Bureau of Biologics, Food
and Drug Administration, and Great Britain's Ministry of Health,
respectively, and under standards of safety and potency defined by
the regulations developed by these agencies. (Note: Because of
a reorganization of FDA accomplished after the Panel submitted its
report, the Bureau of Biologics is now the Office of Biologics
Research and Review, Center for Drugs and Biologics (see 49 FR
10166; March 19, 1984).)

It has become generally understood that a successful and acceptable vaccine must be: (1) safe and (2) effective. Safety means that the preparation used must not cause the disease against which it is directed and that the occurrence of reactions, both local and general must be within acceptable limits. Efficacy implies a useful degree o clinical protection: in some infections, the best guide to immunity the amount of circulating antibody in the blood against the causative agent. It is the clinical trial, however, which must provide the fin critical assessment of the efficacy and safety of the new vaccine. T basic requirements of field trials meeting modern critical criteria were well described by 1957 by W. C. Cockburn, and are elaborated upo in the Panel's generic statement on the requirements for a well-controlled field trial.

The World Health Organization, which was established in 1948, encouraged international cooperation in solving health problems and l been helpful in continuing with the work on establishing and promotir international standards for biological products which had begun with work of the League of Nations.

The growing sophistication of the standardization of vaccines ultimately resulted in changes in Federal law and regulations whereby this Panel was established to help to determine whether currently lic vaccines produced according to specified standards of potency are bot safe and effective for human usage. Although the aims of the act are praiseworthy and the action timely, the judgment concerning safety ar

efficacy of bacterial vaccines and toxoids presents some complex and knotty overall problems.

2. Overall problems--a. Determination of safety--(1) Risk/benefit assessment. The concept of risks and benefits is a fundamental one in a consideration of vaccines, or any other therapeutic or preventive modality. Risks are considered to include the risk of an adverse reaction to the vaccine; benefits, however, include not only the likelihood that a vaccine will protect against a disease, that is, its efficacy, but also that it will ameliorate the severity of the disease to be prevented. Greater risks of adverse effects might be tolerated for a vaccine that provided protection against a lethal disease than for a vaccine against a disease that is basically benign. Furthermore, "benefit" may extend not only to the recipient of the vaccine, but in some cases to society at large.

The risks versus the benefits of the vaccines covered in this report are, like other features of these vaccines, very diverse. Standards of safety must again be individualized for each kind of vaccine. For example, tetanus toxoid is among the safest of all vaccines and its benefits are enormous. Attempts to reduce its reactivity further must not, therefore, jeopardize its efficacy. Although the benefits of pertussis vaccine in infants have occasionally been questioned, the preponderance of expert judgment is definitely favorable. But this vaccine is highly reactive and very justifiable attempts to reduce its reactivity by purification are virtually thwarted by the dependence of the assessment of efficacy upon a mouse protection model which must be linked to

clinical trials to confirm its validity. Despite the vaccine's hazards, therefore, attempts to modify it to improve its tolerance are difficult with present knowledge.

Risk/benefit assessments vary not only between one generic group of vaccines and another, but within a generic category, each product must be assessed individually for its special features that vary from the norm. In addition, some products were modified without updated evidence of their clinical efficacy. In some very uniform vaccines, such as tetanus toxoid, a relatively minor change in production to achieve greater purification or a decreased concentration of toxoid to reduce reaction rates was examined by the Panel very critically because of the need to ensure that the vaccine performed at its expected high level of protection.

The concept of risk/benefit also includes the public's as well as the individual's protection. A vaccine that produces considerable discomfort and sometimes even severe general reactions is more accept-able if the protection it affords the individual also results in pro-tection of the community by reducing contagion. Such is the case in vaccination against pertussis, a contagious disease particularly dangerous to very young infants but dramatically controlled by a rather reactogenic vaccine. In contrast, cholera vaccine exerts little or no effect on the prevalence or spread of the disease and acceptance of its reactions is limited.

(2) Adjuvants. In the course of its deliberations, the Panel was informed by the Bureau of Biologics of the results of studies of the

effect of injection of aluminum adjuvants into special strains of white mice which have a very high natural incidence of fibrosarcoma of the skin. Such mice have been used in some screening studies for the oncogenicity of certain drugs. The experiments showed some enhancement in the rate of formation of fibrosarcomas in the mice that received aluminum adjuvants. The Panel asked for expert interpretation of the design and results of the mouse studies by scientists from the National Cancer Institute and Roswell Park Memorial Institute. These consultants concurred with the Panel in their opinion that the mouse findings were indeed reliable for the design of the experiments but that the significance of the findings for man could not be assessed from this model alone and that studies in other mammalian species should be made.

The Panel therefore surveyed data in man on fibrosarcomas in different populations from various cancer registries. These show that fibrosarcoma is a rare tumor, the incidence increasing sharply in old age. Cohorts were analyzed who were probably exposed to aluminum adjuvants, such as males born around 1920 who probably received immunizations during World War II, whereas the women generally did not. No increased rate of sarcoma in males in that cohort was detected. Because most Canadian vaccines do not contain aluminum adjuvants, mortality rates in Canada were compared with those in the United States for fibrosarcomas. Rates of connective tissue tumors were slightly higher among United States than Canadian males, but the rates for females were similar. The data did not disclose any major differences that would cause concern

over the use of aluminum adjuvants whose benefits are considered to be of major value in the primary immunization of children with DTP vaccines. The Panel encouraged further studies on adjuvants, especially retrospective studies in humans, but did not consider that their recommendations for the safety and efficacy of DTP vaccines containing aluminum adjuvants should be modified at this time.

(3) Liability and legal problems. Almost any clinical investigation to improve well established and highly beneficial vaccines, or to assess more accurately their current reaction rates, is frustrated by the threat of malpractice suits and claims for damages against manufacturers. Physicians who administer vaccines as well as those who produce them feel threatened when reporting adverse reactions, even when the vaccine has been prepared and used in accordance with government regulations and recommendations. Moreover, some reactions are intrinsic to the process of human immunization and range from psychic trauma to fatal idiosyncratic reactions that are extremely rare and are an unavoidable hazard of introducing foreign substances into humans.

The United States has been backward in its failure to deal with the risks and responsibilities of immunization. Several European countries and Japan have established a public compensation system under which their governments have accepted responsibility for the recognized hazards of immunization. Some of these laws provide for compensation from public funds to patients suffering damage from vaccinations that are recommended by competent authorities. Damages have been paid as pensions.

The differences between the primary responsibility of the manu-facturer and the ultimate responsibility of the State should be distin-guished. The former should comply with the regulations of production and marketing procedures. If these obligations are fulfilled and the vaccine is administered correctly, responsibility for immunization accidents should rest with the official agencies recommending them. Unlike many other countries, the United States has not dealt adequately with this issue of immunization, and attempts to improve vaccines further will be hampered. Furthermore, collection of data to establish the efficacy of some of the current licensed products may also be hampered by this deficiency of public policy in the United States.

b. <u>Determination of efficacy</u>--(1) <u>The diverse immunologic actions of the vaccines</u>. The various vaccines that have been lumped together for this Panel's review are so diverse that standards of efficacy that apply to one may not apply to another at all. Progress in immunology is far greater in areas relevant to the effects of some vaccines compared to others. For diseases in which immunity depends upon specific anti-bodies which either neutralize toxin or which opsonize bacteria and lead to their prompt destruction within phagocytes, induction of such anti-bodies correlates well with protection, and the measurement of such antibodies may reflect efficacy quite faithfully.

In many other kinds of antibacterial immunity, however, survival of organisms within cells after ingestion is a particular feature of the host-parasite contest. In these infections the role of cellular immunity

is critical. Diseases such as tuberculosis and typhoid fever are illus-
trative of infections that may be considered intracellular as well as
extracellular. Our knowledge of immunity in such diseases still awaits
greater understanding of the cell-mediated defense process. The effects
of vaccination therefore remain empirical in these diseases and can be
established at present by field trials alone. In pertussis, for example,
the relative roles of humoral and cellular immunity are not at all clear,
and the antibodies that can be measured may or may not be protective.

Finally, protection against a disease such as cholera has been
proven in recent studies to depend primarily upon the prevention of the
attachment of the cholera vibrios to the surface of intestinal epithe-
lial cells. The solution of this problem appears more feasible than the
more complex antibacterial immunity of diseases like typhoid fever.

(2) Establishing standards of efficacy. It should be apparent
that a standard of efficacy must be applied separately to each vaccine
according to current expectations of its performance. For example, for
the prevention of tetanus an almost perfect performance can be expected.
Moreover, its efficacy can be quite accurately assessed by serum anti-
toxin levels. For diphtheria, the standard of efficacy is also high,
but there is less certainty as to what level of antitoxic immunity
constitutes adequate protection because strains of diphtheria may vary
greatly in the amount of toxin they can produce, and absolute immunity
based on a given level of antibody is less predictable.

A major dilemma repeatedly faced by the Panel was the decision whether to place a given product in Category I or Category IIIA. The law requires that each product be proven to be both safe and effective in man; for many products, licensed prior to the current, more stringent legislation, specific data related to efficacy are not available. Even in the absence of such data, however, the Panel has little doubt that the efficacy of tetanus and diphtheria toxoids are satisfactory because it is reasonable to infer that if they were not satisfactory, the remarkable reductions in tetanus and diphtheria associated with widespread use of these vaccines surely would not have occurred. Moreover, the techniques of production suggest that they should be efficacious.

But the charge to the Panel was to examine each licensed product from the standpoint of the scientific evidence that each is both safe and effective in humans. The various toxoids placed in Category IIIA by the Panel are believed to be entirely acceptable in terms of safety. The Panel believes that many are effective, but in the absence of recently obtained proof in humans for certain specific products, the Panel's charge to affirm the effectiveness of individual products could not allow a Category I assignment.

The feasibility of obtaining efficacy data is technically simple in the case of the toxoid vaccines (tetanus and diphtheria) because serum neutralizing antibodies are readily measurable and these reflect efficacy accurately. Blood samples from relatively small numbers of healthy volunteers (se prototype model for study with 20 to 40 individuals) who receive immunization

can therefore establish efficacy. Obtaining blood samples from healthy

volunteers receiving licensed vaccines, particularly children and infants,

is a problem currently complicated by recent regulations on informed

consent. However, the difficulties which may be perceived in obtaining

such data do not outweigh the importance to the public of assuring the

efficacy of these universally administered vaccines in achieving primary

immunization. For these reasons, the Panel recommends that products for

which the human data requested are not available be assigned to Category

IIIA.

In the case of pertussis, the situation is peculiar. Though the

vaccine is a very effective one, it is quite crude, consisting either of

killed whole cells or of a soluble product of the organism. The nature

of immunity is unknown. The disease has almost disappeared in the

United States, making field trials, at least in this country, im-

possible. The standard of efficacy is tied to a highly artificial mouse

model of protection--one that bears essentially little similarity to the

natural disease in man. Yet the last successful field trials conducted

decades ago are tied to current products whose toxicity represents the

major concern about the vaccine. Any move to make the vaccine safer by

modifying it is fraught with the danger of altered efficacy which cannot

be adequately assessed without an extensive field trial.

The plague and cholera vaccines place the Panel in the apparently

inconsistent position of classifying them as effective without the

extensive efficacy data that are available for other vaccines. These

vaccines are of decidedly limited value. At the same time, the Panel
demands of tetanus updated data on antibody levels when relatively small
changes in the vaccines have been introduced recently into the manufac-
turing process. The expectations of efficacy from the current plague
and cholera vaccines are obviously quite different from those expected
from tetanus.

Finally, standards for judging efficacy of currently available BCG
vaccines are far from satisfactory. No reliable animal model or immuno-
logic test has yet been discovered that accurately reflects human
immunity; nobody can prove that the live vaccine strains have remained
unchanged by repeated passage in the laboratories where they are main-
tained; and only new field trials that are in progress but are several
years from completion can determine efficacy. Even then such efficacy
would have to be related only to the strains used in the trial. Nonethe-
less, decisions have to be made based on past performances and to some
degree upon the assumption that the strains of current vaccines are
retaining their immunizing power. Lacking other alternatives, the
decision for efficacy was made by the Panel with full knowledge of the
assumptions that were made.

(3) Extrapolation of data from the use of combined vaccines.
Practical considerations in the evaluation of efficacy for some products
when data were unavailable made it desirable and sometimes necessary to
extrapolate from data on the use of combined vaccines. This approach

appears to be logical and valid, particularly for diphtheria, tetanus, and pertussis vaccines, because of the wide use of the combined diphtheria, tetanus, and pertussis vaccines and the endorsement of this immunization practice by all leading biomedical experts in this country. Accordingly, the Panel made use of the following extrapolation models whenever it seemed appropriate because of the availability of data:

1. Diphtheria tetanus and pertussis (DTP) could provide efficacy data for pertussis (P) (but not for diphtheria (D) and tetanus (T) due to adjuvant effect of pertussis).

2. Tetanus and diphtheria (Td) could provide efficacy data for T and also possibly for diphtheria and tetanus (DT) and D if the small 2 Lf dose of DT in Td proved adequate. Caution would be necessary in extrapolating Td data in adults to children 6 years of age or younger.

3. DT could provide efficacy data for D, T, and for the T component of Td.

Combined product available	Would provide efficacy data for:
DTP	P
Td	DT* D* T
DT	D T Td (T-only)

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*If response of 2 Lf Diphtheria toxoid were satisfactory, the larger amount in "D" products could be assumed satisfactory.

(4) <u>Patient participation, informed consent, and clinical trials</u>.
When sufficient data were not available from which to determine efficacy,
the Panel had to consider the feasibility and cost benefit of the required
further clinical investigation. Such factors stimulating the Panel's
desire for more data were: (i) changes in the manufacturing process,
the concentration of antigen, the purification of the product, or the
additions of preservatives or adjuvants; (ii) the dependence of some
manufacturers upon clinical data establishing the effectiveness of the
same vaccine made by others; (iii) possible changes in the state of
immunity of the population and secular changes in the epidemiology of
the disease; (iv) the need for better products or immunization sched-
ules to increase efficacy or decrease reactivity.

On the other hand, the Panel was mindful of the growing diffi-
culties of obtaining participants and informed consent for clinical
trials--even those as simple as obtaining a few samples of blood per
patient by venipuncture. For primary immunization trials, the need to
obtain consenting subjects who have no prior immunity imposes a further
stringent limitation. If clinical trials were to require more than an
assessment of humoral responses, the inability to evaluate protection
against a challenge of natural disease in this country (such as in the
case of tuberculosis or pertussis) made insistence upon such data unreason-
able. The dilemmas of inadequate clinical data to judge efficacy versus
limited access to such data led to productive discussions and workshops
with manufacturers and the Bureau of Biologics to establish efficient

and relatively standard protocols which would supply the required data from minimal numbers of participants and at minimal costs. The Panel's general recommendations contain suggestions arising from these conferences.

(5) Animal models. Animal models of the human diseases in which vaccines may be accurately and reliably assayed for safety and efficacy would solve many problems of clinical investigation and human trials. The Panel found this need particularly cogent in the case of pertussis and tuberculosis in which animal models were inadequate and field trials not feasible. In these instances recommendations that vaccines be classified in Category IIIA to obtain further proof of safety and efficacy will be greatly handicapped unless animal models are developed which correspond closely to the human disease counterpart.

(6) Administrative problems. Several administrative problems had to be solved by the Panel to carry out its charge and mission. Some licenses had been held on products which the manufacturers had not marketed for many years. Some of these products were intended to be used only when the vaccine was combined with others (for example, monovalent diphtheria toxoids). Some antiserums (equine diphtheria antiserum) and some toxins (diphtheria toxin for Schick testing) were considered useful for limited purposes only. They might be in limited supply, therefore, unless publicly subsidized. During the course of the Panel's review, licensed products were updated because of modifications, and license applications were amended to replace outdated products (for example, plague vaccine).

(7) Related issues. Careful attention was given to the opinions
and policies of other governmental agencies and professional societies
concerning the safety, efficacy, and recommended usage of the vaccines
reviewed. The Panel was mindful that its decisions were concerned
primarily with assessing evidence of safety and efficacy of the vaccines
rather than determining either public health or clinical practice policy
governing their usage. It was gratifying, however, that very few signif-
icant differences of opinion were encountered among recognized authori-
ties. The most divergent opinions related to the issue of the efficacy
of the BCG vaccines and reflected the need to establish whether or not
prolonged storage and passage of the seed strains in laboratories had
led to changes in their efficacy. Limited enthusiasm for the use of BCG
by public health authorities in the United States as a means for the
control of tuberculosis had to be weighed against: (i) evidence of
efficacy; (ii) alternative strategies for control; and (iii) the right
of manufacturers to produce and physicians to use a vaccine, if effec-
tive, in some parts of the world and in some populations of the United
States with unusual risks of exposure to tuberculosis. Although some
would have preferred a "Category III" classification for BCG, requir-
ing updated clinical data of efficacy, the feasibility of obtaining such
data in the ensuing several years appeared remote and unnecessary at
this time when weighed against the favorable evidence for BCG. The
Panel was faced with having to make an "effective" versus "ineffective"
judgment on the basis of the evidence at hand and the evidence, although
incomplete, clearly called for a judgment of effectiveness.

3. <u>General recommendations--a.</u> <u>Support for widespread immuni-</u><u>zation programs.</u> Universal active immunization for the prevention of tetanus, diphtheria, and pertussis should be accomplished to take full advantage of the great effectiveness of these vaccines and to obviate the inherent risks, cost, and effort of passive immunization which is incompletely effective in the first two diseases and not effective in the third.

b. <u>Liability legislation for immunization.</u> Assessment of the safety of vaccines requires improved procedures for reporting adverse reactions. This in turn requires the development of a more enlightened public policy which includes acceptance by the U.S. Government of responsibility for the recognized and unavoidable hazards of immuni-zation.

Legislation is urged that will provide compensation from public funds to individuals suffering damage from vaccinations that are recom-mended by competent authorities, carried out with vaccines that passed official safety and efficacy review, and that were administered by recommended techniques. Such legislation will not only greatly improve assessment of safety but will also enhance collection of the data necessary to establish efficacy by reducing the professional liability issues in clinical investigation of vaccines.

c. <u>Improved efficacy of clinical investigation.</u> The Bureau of Biologics should offer guidance to manufacturers with regard to recom-mended protocols which would help to provide adequate clinical data for

assessing vaccine efficacy. Because of the increasing difficulties in obtaining informed consent to conduct studies on normal individuals, even studies requiring no more than serial venipunctures, it would be most efficient and economical to develop protocols that would provide required information with the fewest numbers of participants and specimens. These considerations are especially appropriate in studies involving children. Cooperation among manufacturers and the Bureau of Biologics should be promoted to adopt relatively standardized protocols that might set minimum limits to the numbers of individuals required to achieve statistical strength of data and appropriately controlled conditions, laboratory methods, and population groups.

Currently there is a conflict between the public's need for precise data regarding the safety and efficacy of immunization programs and the rights of the individual, both in terms of experimental risk and privacy. Despite the need to protect the privacy of the individual, a mechanism should be developed that would provide means of access for authorized investigators to demographic and health data on individuals in order to conduct long-term followup studies of immunization procedures.

d. Improved production procedures. Some standards of purity, immunogenicity, and immune responses for well-established vaccines are based upon old-fashioned methods that should be updated by more sophisticated techniques made possible by advancing scientific knowledge. Efficacy and safety should be assessed and defined in terms of more

modern standards of quantitative immunobiologic testing, chemical puri-
fication, and clinical evaluation. The motivation and impetus to accomp-
lish this is unlikely to come spontaneously from pharmaceutical manu-
facturers unless review of vaccine licensure is conducted periodically.
In addition, workshops should be promoted regularly by the Bureau of
Biologics to encourage progress in methodology and to coordinate further
efforts at standardization.

e. Research priorities--(1) Animal models. There is great need
to develop animal models that accurately predict vaccine responses in
man. Throughout the Panel's review, one of the most frequently re-
curring problems was the need to minimize our dependence on the labori-
ous collection of expensive and often virtually unobtainable clinical
data in order to determine efficacy. Manufacturers are not primarily
responsible to implement the quest for animal models, and the develop-
ment of such models will require public research support.

(2) Laboratory tests and procedures. Increased emphasis is
needed on the development of laboratory tests and procedures that
reflect vaccine efficacy with sufficient accuracy so as to minimize the
need for field trials. Improved immunologic tests, the use of tissue
culture assays, and relatively simple, reliable, and low-risk clinical
procedures, such as skin tests, would simplify clinical investigation of
vaccine efficacy.

(3) Collaborative and cooperative studies. Collaborative and
cooperative studies should be encouraged particularly when such group
efforts at collecting data may reduce the cost and effort and increase

the availability of opportunities for clinical investigation, or may resolve quickly and efficiently such issues as dose schedules and the frequency and intervals of injections of vaccines within a generic group that are comparable in potency.

(4) <u>Areas of limited knowledge concerning effective vaccines</u>. Support is needed for research in areas where knowledge of the mechanisms of immunity is limited. It is possible that the judgment of a vaccine as safe and effective may actually discourage research by lowering the apparent priority for the need to improve the vaccine. In diseases such as pertussis, typhoid fever, and tuberculosis, the mechanisms by which immunity is produced and the specific antigens that are responsible for the induction of immunity and for reactogenicity are poorly understood. Further research efforts to reduce the toxicity of these vaccines and to improve their effectiveness will require specific public support.

(5) <u>Increased efficiency of effective vaccines</u>. Support should be available for clinical investigation in areas of vaccine research where it is likely that further progress can be made even where a high degree of vaccine efficacy already exists. An example would be the improvement of the already very safe and effective tetanus vaccines by reducing the number of injections required to achieve primary immunization.

(6) <u>Unmet needs</u>. Finally, research is needed to fulfill unmet needs in protection against bacterial infections. Streptococcal, staphylococcal, gonococcal, hemophilus, and pseudomonas infections, to name but

a few, are potentially preventable by immunization. Moreover, there are some products that are needed and can probably be prepared but are not available now, such as botulinus human immune globulin and diphtheria human immune globulin.

f. Assurance of vaccine availability. Close surveillance is necessary of certain vaccine products whose ongoing production in the United States may be discontinued or suspended for commercial reasons despite current or potential needs. Diphtheria toxin for Schick testing and equine diphtheria antitoxin for the treatment and passive immunization of diphtheria are two examples. Continued interaction between the Bureau of Biologics and the Centers for Disease Control should be encouraged to ensure government stock piling of required products that are no longer produced commercially.

In addition, some products are produced solely by foreign firms. The Istituto Sieroterapico Vaccinogeno Toscano Sclavo pharmaceutical firm in Italy is a major source of diphtheria antitoxin, and the status of diphtheria antitoxin produced in the United States is uncertain. Connaught Laboratories of Canada is the only producer of trivalent botulinus antitoxin. Furthermore, a major vaccine produced by a single domestic firm represents an inherent danger, in that the public is dependent upon a limited source without well-defined mechanisms for the control of production and supply.

Public policy needs to be formulated more thoroughly in the entire area of production and supply of vaccines. Prospective planning and

negotiation between public agencies and the pharmaceutical industry should be established as a process by which to ensure vaccine availability when the market alone is inadequate to accomplish this end. Consideration should be given to the establishment of a National Vaccine Commission which can address itself to the solution of these problems.

g. Improved reporting of adverse reactions. At present, there are virtually no standards set for what constitutes untoward reactions to vaccines except their most severe and dire complications; therefore, it is difficult to document the actual reactogenicity of some products. Standards for "threshold reactions" above which reports are required need to be established for each generic group of vaccines. The Study Commission on Drug Use, which is studying adverse drug reactions, should be urged to consider reactions to biological products as well.

h. Improved labeling. Review of the labeling of products submitted to the Panel identified a number of deficient areas in which substantial improvement should be made. A standard for adequate labeling along the lines outlined by the generic labeling statement of the Panel should be adopted so that the accuracy and readability of all labeling can be brought to an optimally useful level.

i. Improved administrative procedures--(1) Periodic review of all licensed vaccines. Periodic review of all licensed vaccines should be carried out to assure that the safety and efficacy of these products are kept current and that standards of production and assay are modernized.

(2) <u>Limited term for vaccine licenses</u>. By limiting the period for which vaccines may be licensed, all products, old and new, will be assured regular review. Furthermore, new vaccines that have only limited evidence of efficacy or for which the clinical efficacy data needs to be extended by further experience (situations in which we now assign "Category IIIA," i.e., insufficient data but probably effective) should be provisionally licensed for only limited periods of time within which additional data can be generated.

(3) <u>Revocation of licenses for nonmarketed vaccines</u>. Some products that have not been marketed for many years are still licensed, and it is not known whether they would still qualify as safe and effective products if and when production is resumed. Some products have never been marketed in the form for which they were licensed. In the light of current efficacy review standards, it would be better policy to revoke such licenses and require reapplication when necessary.

(4) <u>Consistency of efficacy data</u>. Protocols for efficacy studies should be reasonably consistent throughout the industry for any generic product and should employ standard tests, standard procedures for conducting tests, and standard reference sera. It would be advantageous to develop industrywide, consistent, standardized guidelines for adducing required data. Such standardized procedures may need review and updating periodically, as new improved laboratory tests become available.

j. <u>International cooperation</u>. The Panel recommends that international coordination of vaccine standardization and assessment of

safety and efficacy be encouraged through groups such as the World
Health Organization, the International Association for Biological Stan-
dardization, and between ministries of health of various countries. In
many instances the assessment of vaccine efficacy may be possible only
in those countries where an opportunity for field trials may exist.

k. Role of review panels. Judging from the experience of the
Panels during their reviews, their current roles as advisory groups
should be extended so that they may continue to serve to help assess
future safety and efficacy issues that arise with new or improved
vaccines.

l. Privacy of panel sessions. The Panel has had little problem
in performing its functions at open sessions and believes that closed
sessions are necessary only to protect the rights of confidentiality to
which license submissions are entitled. The Panel also has had no
objection to having its sessions taped and recorded.

m. Transcription policy. The cost/benefit of verbatim trans-
cription of the entire deliberations of the Panel, especially those that
lead to a documented report, is, however, very limited. Verbatim trans-
cription of the vast amount of tedious and noncontroversial detail
covered in reviews is enormously wasteful, inhibits free, relaxed, and
creative discussion and exposes Panel members to the risk of remarks
and opinions that may be only tentative and that may be quoted out
of context.

4. Summary of unresolved problems. In concluding its report, the
Panel deems it important to call attention to some of the major unre-
solved problems that have made its advice and decisions most difficult

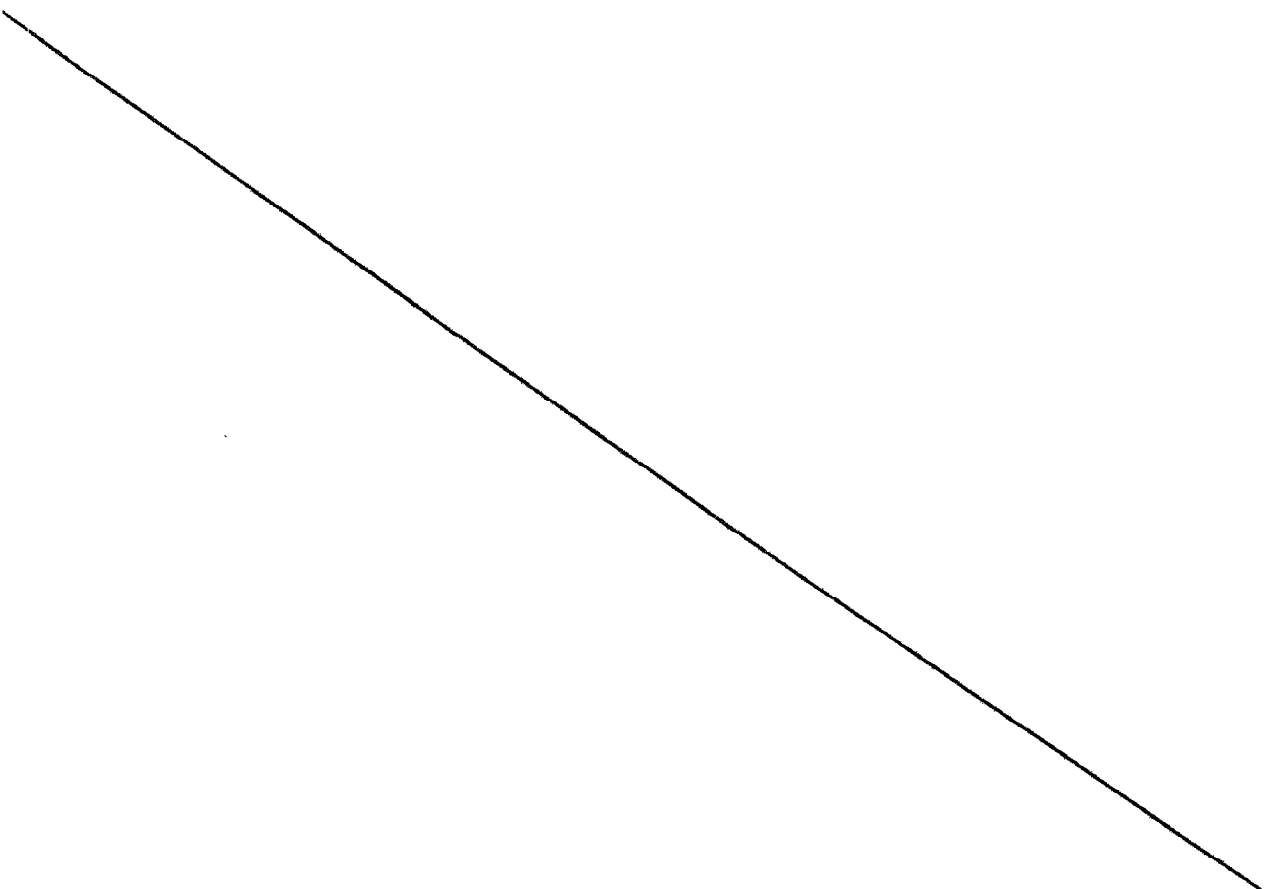and that will continue to hamper the assessment and the improvement of the safety and efficacy of vaccines.

a. Emphasis upon proof of efficacy and upon critical standards of the scientific quality of vaccine data may inhibit the motivation to modify and improve current vaccines and to introduce new ones. If rigid and critical standards are to be set and met, much effort should be put into finding efficient and effective ways to encourage and expedite the conduct of such research.

b. The complexity of the legal and administrative procedures deemed necessary to ensure the protection of the rights of individuals participating in clinical investigations impose serious restraints to the acquisition of vaccine efficacy data, because such studies are usual undertaken in normal individuals and often, in the case of universally administered vaccines, in relatively low risk groups. Public policy will have to be formulated to provide incentives to both clinical invest gators and participants to engage in the carefully designed field trials and other controlled experiments that are now required. The U.S. public should share as a whole in the responsibility to participate in such studies. As previously noted in section 2.b.(2) of this preamble, the difficulties that may be perceived in obtaining such data do not outweigh the importance to the public of assuring the effica of these universally administered vaccines in achieving primary immuniza tion.

c. Standards of efficacy will have to be evolved for products that are not amenable to clinical trial (e.g., botulism antitoxin).

d. Emphasis upon the individuals' rights of privacy of personal health data can conflict with the public's need for data on immunizations which requires access to health records. Specific exceptions will have to be written to the laws protecting confidentiality of public health information, which is now regarded as private.

e. Finally, the glaring absence of a coordinated national immunization policy that would efficiently implement and expedite vaccination procedure and vaccine development, production, and supply is now apparent Such a policy should be formulated without further delay so that future decisions on vaccine safety and efficacy can be made with greater assurar of public acceptability and support.

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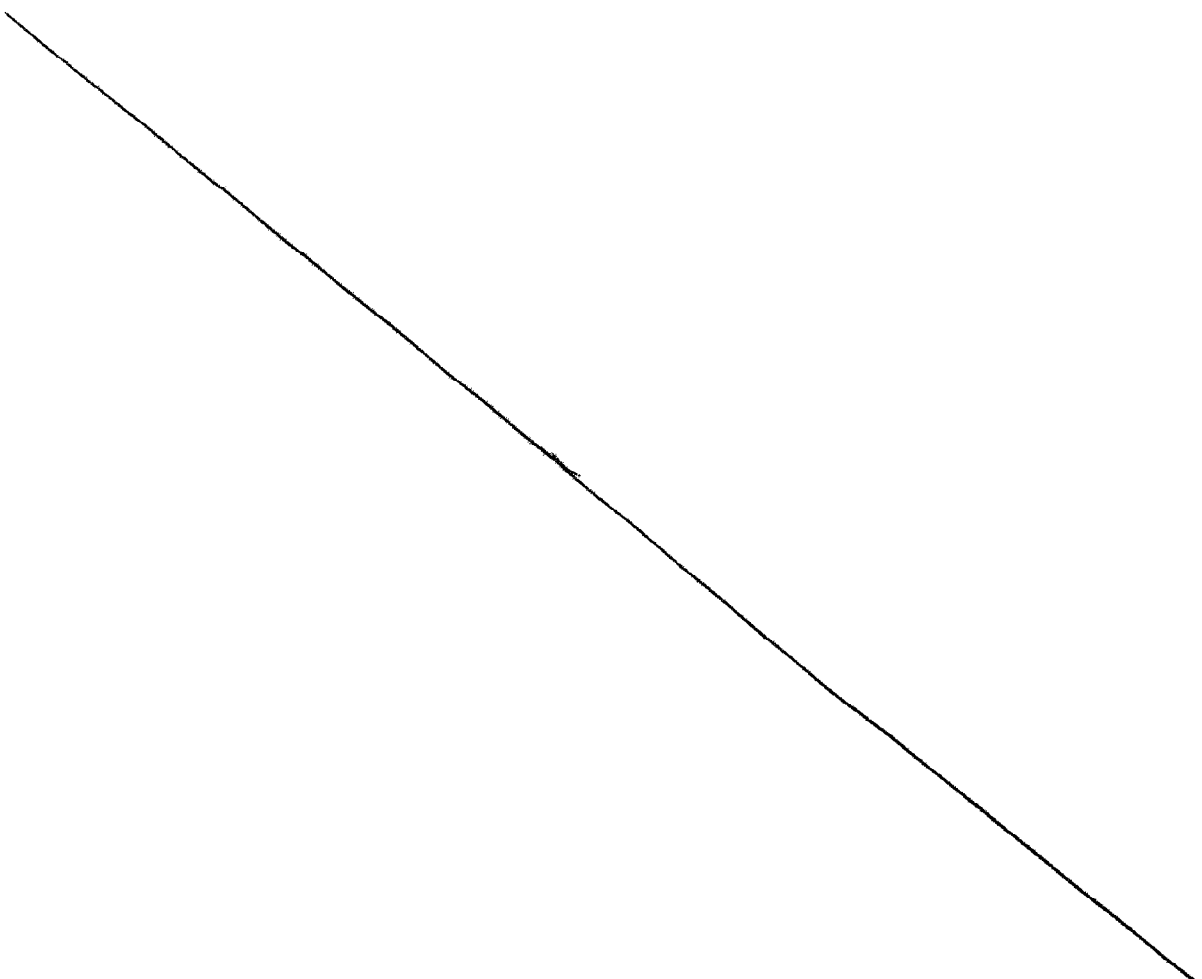
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LABELING

Review of the labeling of products submitted to the Panel on Bacterial Vaccines and Toxoids identified a number of deficient areas in which, in the judgment of the Panel, substantial improvement should be made. The following generic comments on the subject of labeling highlight the view of the Panel on what constitutes adequate labeling, and provides a standard such that all labeling can be brought to an optimal level.

General Comments

Labeling should meet the following general criteria:

The labeling should be written in clear English. In many instances current labeling is written with very complex sentence structure. There is very often marked ambiguity of meaning. In some instances, even Panel members charged with reviewing the subject were unable to determine the precise meaning of statements in the package insert; the physic: who may be expected to give the labeling little more than a cursory reading therefore may often receive inadequate guidance.

The labeling should be easily legible and printed in such a fashion as to attract, rather than to repel or discourage, the reader. Much of the present labeling is printed in type so small as to discourage all but the most determined reader.

The labeling should contain a summary of the essential scientific information the physician needs to use the bacterial vaccine or toxoid safely and effectively in the care of patients. It should be informative, accurate, and nonpromotional in tone.

Labeling should be reviewed and revised as necessary at intervals of no more than every 2 years. The date of last revision should be clearly identified in the label. Although the area of bacterial vaccines and toxoids has not been marked by rapid and dramatic advances resulting from medical research, immunization practices do evolve gradually with time and in the light of new data or circumstances. Many of the recommendations contained in the labeling of products currently on the market are out of step with current practice and recommendations. Bibliographic citations should similarly be revised and updated at intervals of no more than every 2 years.

Labeling should ordinarily contain information in the following format and order:

Description

Clinical Pharmacology/Biological Activity

Indications and Usage

Contraindications

Warnings

Precautions

Adverse Reactions

Overdosage

Dosage and Administration

How Supplied

The Panel has reviewed and concurs with the proposed format changes as described in the statement on "Labeling of Prescription Drugs Used in

Man" (21 CFR Part 200), previously circulated by the Food and Drug Administration. The following comments presume the adoption of these new standards, follow the same recommended format, and reflect the Panel's particular concerns in the labeling of bacterial vaccines and toxoids.

Description

This should be a concise statement of the method of preparation of the product, the characteristics of strain or species used, the scientific name of the bacterium, noting the specific strain if important, the process used, the potency standard that has been met, the antigenic content of the product, the stabilizers and preservatives included, and the suspending menstruum. Terms such as "purified" and "refined" are more promotional than scientifically meaningful. An accurate statement of the precise process that is used would be considerably more meaningful.

Clinical Pharmacology/Biological Activity

This section should contain a concise factual summary of the immunological response to the product in terms of immunity, antibodies, or other parameters. Specific points to be covered, when applicable, include The proportion of individuals in which antibody will be produced, the number of doses required to produce satisfactory levels of antibody, techniques and reliability of antibody measurements, the time at which antibody is detectable, peak antibody levels to be expected, expected decay of antibody titers, and the degree and duration of protection to be expected. Concise summary description of data in support of the efficacy of the product in animals or in man should also be included.

Indications

The indications should be stated as specifically as possible.
Liberal use should be made of the recommendations of official bodies
such as the Public Health Service Advisory Committee on Immunization
Practices, Center for Disease Control, the Infectious Disease Committee
of the American Academy of Pediatrics, and the American Public Health
Association. (Note: Subsequent to the Panel's completion of this
report, the Advisory Committee on Immunization Practices was renamed
as the Immunization Practices Advisory Committee and the Center
for Disease Control was renamed as the Centers for Disease Control.)
The specific recommendations of these advisory groups
should, if appropriate, be reprinted in their entirety in the labeling.
The number and frequency of injections of a given antigen(s) should be
specifically stated. If products containing more or fewer antigens as
combined products (e.g., DT, DTP) are preferred for a specific purpose,
this should be so stated in this section. In such a case, the circum-
stances should also be defined when the product under consideration
should be used rather than the preferred product. Where appropriate,
labeling should also point out the generally accepted superiority of
adsorbed vaccines and toxoids over comparable fluid products.

Contraindications

This section should state those situations in which the agent
should not be used because the risk of use clearly outweighs any possi-
ble benefit. Such situations include administration of the agent to
patients known to have a serious hypersensitivity to it and use of the
agent in patients who, because of their particular age, sex, concomitant
therapy, disease state, or other condition, have a substantial risk of
being harmed by it or not receiving the expected benefit from it. This

section should list known hazards, and theoretical hazards, if mentioned, should be identified as such. The Panel encountered in its review a number of labels in which it appeared that producers were overly concerned about protecting themselves, rather than the patient.

Warnings

This section should state serious adverse reactions and potential safety hazards, limitations of use imposed by them, and steps which should be taken if they occur. This section should describe any unusual circumstances relating to the use of the product, including particularly any circumstances under which use of the product may be hazardous or less effective. The specific circumstances and the specific hazards should be described fully.

Precautions

This section should contain the following subsections as appropriate for the product;

1. General. This subsection should list any special care that should be exercised to permit safe and effective use of the product by the physician.

2. Clinical and laboratory tests. This subsection should list those laboratory tests that may be needed to follow the patient's response or to identify possible adverse reactions.

3. Special instructions to be given the patient. This subsection should specify instructions for patients to achieve safe and effective

use. Any patients' brochure or printed instructions to vaccinees should be reprinted under this section heading.

4. Clinically significant product interactions. This subsection should provide specific practical guidance to the physician on avoiding and/or managing clinically significant drug interactions, such as might occur with simultaneous active-passive immunization.

5. Pregnancy. Recommendations concerning the use of the product during pregnancy should be detailed in this section.

Adverse Reactions

This section should contain not only a description of the nature of local and systemic adverse reactions that have been observed following use of the product as recommended, but also their relative frequency. Specific recommendations for management of adverse reactions should also be included in this section, as should recommendations for reporting of adverse reactions to the manufacturer and FDA.

Overdosage

This section should describe the signs, symptoms, and laboratory findings of accidental overdosage and the general principles of management. It should include specific information, if available, on the emergency treatment, antidotes, and the value of any recommended therapeutic measures.
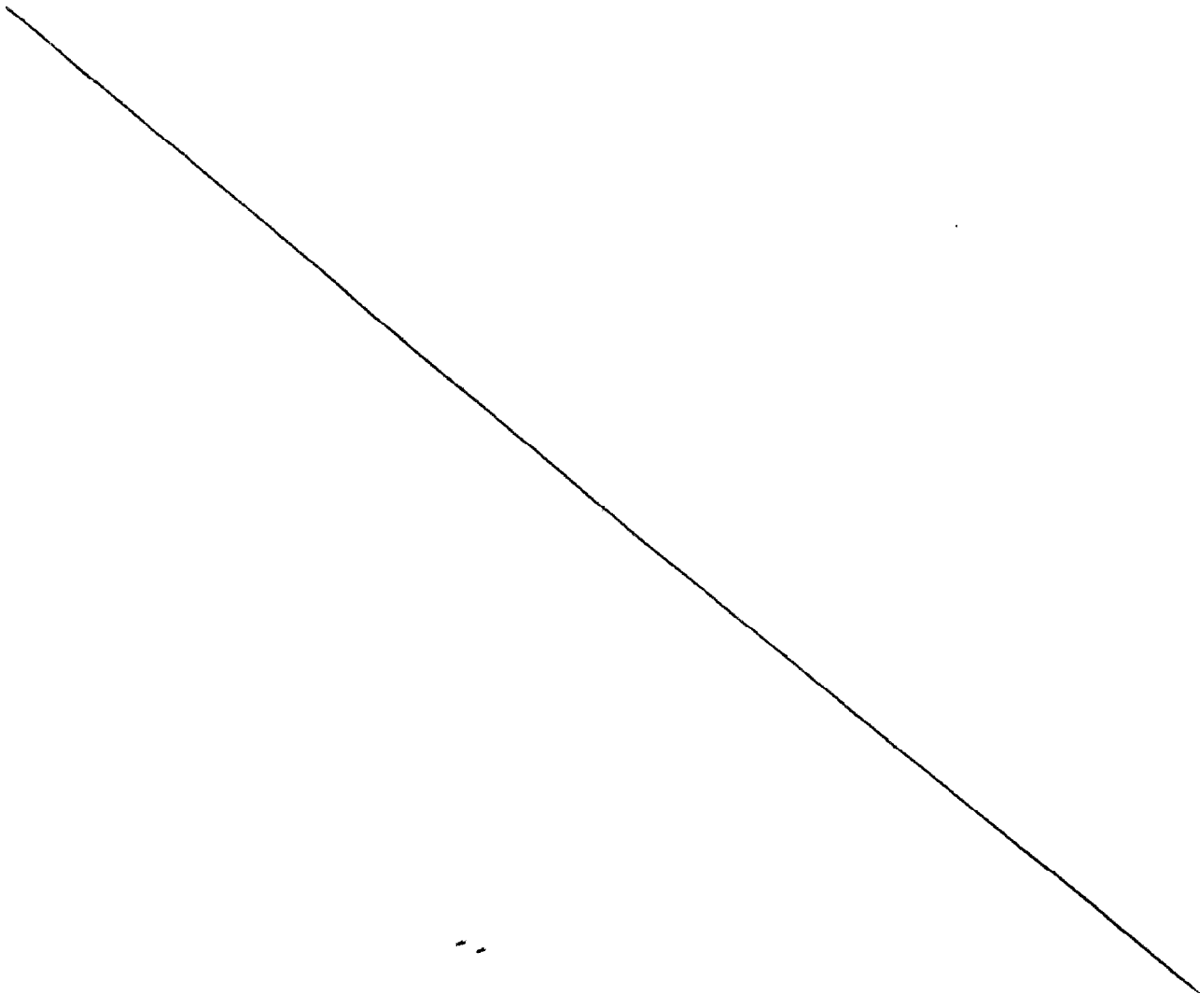
Dosage and Administration

This section should state the usual recommended dose and frequency, and if appropriate, limits beyond which the product should

not be administered.   Precautions against inadvertent intravenous

injections should be included.   It should include the intervals rec-

ommended between doses, and modification of dosage needed in special

patient populations such as infants and children.   Specific tables or

nomograms should be included to clarify dosage schedules.   This section

should also contain specific directions on dilution, preparation, and

administration of the product if needed, and storage conditions for

stability of the product where important.

How Supplied

This section should state the available dosage forms, potencies,

and units of issue of each product to which the labeling is applicable.

GENERIC STATEMENT ON REQUIREMENTS FOR A
WELL-CONTROLLED FIELD TRIAL

Some of the immunizing agents the Panel was required to evaluate had been tested for efficacy only in the first part of the 20th century, when the methodology for obtaining unbiased reliable results in field trials had not yet been fully worked out. Examples of such agents are diphtheria and tetanus toxoids. The respective diseases have declined in incidence, and opportunities for additional field testing for efficacy do not exist in this country.

In developing new immunizing agents, the products are generally first tested in animals for their toxicity and ability to elicit antibody response. When the animal model is suitable, the protection provided by immunization against challenge by the microorganism is also evaluated. Subsequently the immune response in humans is measured, and the dose which induces a seemingly adequate immune response with an acceptable low rate of adverse reactions is sought.

The final and most important step is the field trial, when a large number of presumably nonimmune humans is inoculated, and the incidence of the disease among vaccinees and control subjects is compared.

In the past "historical" controls were frequently employed to test the effects of a new vaccine. By this no-longer-acceptable technique, the frequency of illness in a vaccinated group was compared with the frequency in a similar unvaccinated population at some time in the past. Unfortunately, a decline in disease frequency after vaccination cannot

be interpreted as resulting from vaccination, because the changes may be due to natural disease cycles, to changing socioeconomic conditions, or to therapeutic measures, such as antibiotics.

Also no longer acceptable are comparisons of the frequencies of disease in those who do and do not volunteer for a vaccine study. The fallacy of this approach is that volunteers differ from nonvolunteers in many important aspects. For instance, the former may be more health conscious and inclined towards prevention; they may come from smaller families and living conditions may differ from those of nonvolunteers. Such behavioral and socioeconomic factors may affect the risk of exposure and the host's natural ability to resist infection. Modern scientific methodology requires that volunteers for a study be divided into groups by a randomization procedure, one group constituting the control group, which is given a placebo (inactive, dummy) substance. Randomization is necessary to ensure that the volunteers are distributed without bias, thereby increasing the chances that all variables, known and unknown, that might affect the results of the study are distributed evenly between vaccinated and control groups. Indeed, if the populations are heterogeneous in age, sex, race, or other important variables, it may be necessary to classify or "stratify" them into groups according to these characteristics with randomization within these groups. These rigidly designed experiments, with or without stratification, are called "controlled trials."

An additional requirement in a controlled trial is that the study be carried out double-blind if at all feasible. This implies that both

the study subjects and the observers are unaware of the treatment assigned to the individual in order to ensure unbiased assessment of outcome.

Before subjects are enrolled in controlled trial , ethical considerations require that all the procedures in the studies are explained to them, and that the risks as well as possible benefits are adequately described. The right to withdraw from the study at any time without penalty is pointed out. The rights of the subjects are protected by special committees in all major research centers and by special committees at the Department of Health and Human Services. These committees review the applicable consent forms and the research. All government-sponsored research and virtually all other research involving human subjects requires review by institutional human subjects rights committees.

Whenever practical, in order to provide some benefit to the control group, a vaccine against an entirely different disease, rather than an inactive placebo, is given to the control group.

Assignment to groups is carried out after the subjects have decided on participation, and after the study has been fully explained to them. Participation of children requires special consideration. Consent from parents as well as older children must be obtained.

In carrying out controlled field trials of new improved vaccines, ethical considerations do not allow a placebo assignment if an effective vaccine already exists. Thus, comparison can only be made between those given the new and the old product; enrollment of very large population groups may be necessary in order to distinguish small differences in efficacy.

Analysis of the results of a vaccination study is achieved by "breaking the code" identifying the allocation of individuals to vaccinated or control groups. The code is broken at the end of the study or after an outbreak of the disease has occurred. Under some circumstances it may be desirable for a statistician, who possesses the allocation code but is not participating directly in the study, to examine periodically the results as they accumulate. By this mechanism, called sequential analysis, the study can be interrupted as soon as it has become evident that one treatment or vaccine is superior to the other.

Field trials designed to measure efficacy directly have become increasingly difficult to conduct under conditions of decreasing incidence of natural disease. For this reason, serologic documentation of efficacy must increasingly be substituted in lieu of direct evidence of efficacy. The following protocol is provided to serve as an example of one type of clinical study which would provide reliable information on the efficacy of the product to be assayed as simply and as economically as possible and is illustrative of many of the concepts implicit in the Panel's position regarding well-controlled field trials as well as in FDA's regulations regarding such matters (see 21 CFR 314.111).

SAMPLE PROTOCOL FOR ASSAYING EFFICACY OF TETANUS TOXOID IN MAN

Objective. To determine by a study with the fewest number of subjects and fewest number of bleeds required whether a particular preparation

of Tetanus Toxoid (alone or combined with Diph-
theria Toxoid) produces an acceptable level of
immunity in individuals not previously inoculated
with Tetanus Toxoid. An acceptable level of immu-
nity is defined as:

1. Over 80 percent of subjects having $\geq$ 0.01
International Unit of Tetanus Antitoxin per mL in a
serum sample drawn 10-14 days after basic immuni-
zation (2 injections of adsorbed Toxoid or 3 of
fluid Toxoid) have been given. OR

2. Over 80 percent having $\geq$ 0.1 International
Unit per mL in serum sample drawn 10-14 days after a
reinforcing injection given 6 to 12 months following
basic immunization as defined above.

It is to be noted that 80 percent "success" by
either criterion given above is a minimum tolerated
level; the normal success rate, in many studies
reported over the last 3 decades, is 95-100 per-
cent.

Subjects. The study population should consist
of healthy children or adults of either sex, and
should have acceptable evidence of being primary
responders to tetanus toxoid. In the case of infants
less than 6 months of age, negative immunization

history from a responsible parent or guardian would
be considered acceptable. For older children and
adults, the most valid evidence of primary response
is the absence of serum antitoxin 7 days after
the initial dose of toxoid. In neither instance is
a preimmunization serum necessary. Data from older
children and adult subjects screened for antitoxin
negativity by a zero-day rather than a 7-day bleeding
may be confounded by the inadvertent inclusion of
individuals who are secondary rather than primary
responders.

Numbers. Size of group should be so selected
as to provide serological data on 40 acceptable
subjects at end of study. Sixty is recommended as a
minimum starting number if subjects can be carefully
selected by good histories of no prior Tetanus
Toxoid injections (about 10-20 percent will have had
previous toxoid injections without their knowledge).
However, larger samples, if possible, would be
desirable and might provide more data. Another 10-
20 percent may be expected to drop out of the study
along the way.

Evaluation. On a 95 percent probability basis,
US MIL-STD 105D (Canadian Standard CA-C-115; "Speci-
fication for Sampling Procedures and Tables for

Inspection by Attributes," British Standards Institution, BS 6001, 1972), indicated that the following 2-sample sequence may be used to obtain an answer:

	Accept	Reject
1st sample of 20	1 failure	4 failures
for 2 or 3 failures, go to:		
2nd sample of 20	4 failures	5 failures
(Total of 40)		

ACTIVE IMMUNIZATION PRODUCTS

Generic Statement on Diphtheria Toxoid

Diphtheria is an infectious and communicable disease of man which usually involves the upper respiratory tract and sometimes produces skin infections. The causative agent is <u>Corynebacterium diphtheriae</u>, a gram-positive bacillus with metachromatic granules. Upper respiratory diphtheria is characteristically associated with the production of a pseudo-membrane in the nasal passages, pharynx, and/or larynx, and with the appearance of systemic symptoms due to adsorption of an exotoxin. Fifty years ago there were approximately 200 cases per 100,000 population in the United States each year (roughly 350,000 cases annually). This has decreased to a rate of about 0.1 per 100,000 population in recent years (200 to 400 cases annually). Approximately 10 percent of patients with diphtheria succumb. Death may be due to respiratory obstruction by the membrane or to remote effects of the toxin upon the myocardium or peripheral nervous system.

Because the morbidity and mortality of diphtheria are largely a consequence of the toxin elaborated by the organism, antiserum (anti-toxin) prepared by immunizing horses has been used for nearly 80 years in the treatment of the disease and for its prevention in exposed, susceptible individuals. This approach to control of the disease is only partially successful because the disease is already well estab-lished by the time it is recognized, and toxin that has been adsorbed and fixed to cells is unaffected by antitoxin.

Further, antitoxin does nothing to prevent spread of disease.
Penicillin or other effective antibiotic agents will usually eradicate
the organism, but because they have no effect against toxin, antibiotics
are only an adjunct to therapy.

Since passive immunization with antitoxin and therapy with anti-
microbial agents do not provide a satisfactory approach to the control
of diphtheria, active immunization of humans against the toxin has been
employed for many years (also see Generic Statement on Diphtheria Anti-
toxin). The reduction in morbidity and mortality from diphtheria in the
United States during the past half century is largely attributable to
widespread immunization against the toxin.

Description

Diphtheria toxoid is a cell-free preparation of diphtheria toxin
treated with formaldehyde so that when administered to humans it does
not produce the known toxic effects of diphtheria toxin, but nonetheless
produces a specific immune response to the toxin.

The rationale for this preparation is based on the fact that the
pathogenicity of the Corynebacterium diphtheriae for man is almost
entirely derived from the effects of its exotoxin. Rarely, apparently
nontoxin producing strains of the organism produce disease. Also
uncommon is disease produced by toxigenic strains in individuals immune
to the toxin. In these rare instances, the significance of the disease
is dependent upon local inflammatory response, and not upon systemic
dissemination of toxic products.

Early in this century, attempts were made to devise means by which immunity to the toxin might be induced in man. The potency of the toxin is such that the miniscule amounts that can be safely administered to man fail to induce protection. Indeed, the disease itself sometimes fails to induce immunity in survivors. The first successful preparation for inducing immunity was a balanced combination of diphtheria equine antitoxin and the toxin. Disadvantages included reversion to toxicity when frozen, frequent sensitization to horse serum, and less than optimum induction of the immune state.

Attempts to detoxify the toxin without destroying its antigenicity repeatedly failed because of the instability of the toxoid, until it was shown that formaldehyde treatment of the toxin produced the desired result. Current toxoids are a result of this observation.

Combinations of the formaldehyde-inactivated toxoid with various aluminum compounds have resulted in preparations more antigenic than the fluid (plain) toxoid, and represent the most commonly used preparations in the United States. Such preparations are designated "adsorbed."

Production

A strain of <u>Corynebacterium</u> <u>diphtheriae</u> established as a potent toxin producer is grown in a liquid medium so constituted as to afford optimum conditions for toxin production. The medium must be free of blood products, horse or other animal serum, and any proteins known to be allergenic to man. Removal of bacterial cells and sterilization are accomplished by centrifugation and filtration. The resultant toxin is

tested for potency according to the U.S. standards and is incubated with formaldehyde in established proportions to effect conversion to toxoid. Before or after conversion to toxoid, additional steps are usually taken to purify and concentrate the fluid antigen partially.

Treatment of the fluid toxoid with aluminum compounds is employed utilizing established techniques to produce the adsorbed product. A preservative (usually thimerosal but never phenol) is added.

The amounts of toxoid present in preparations are specified in flocculation units (Lf), measured by established techniques.

Use and Contraindications

This product, used for active immunization against diphtheria, is rarely indicated as a single toxoid, either in the fluid or adsorbed form. For primary immunization of children younger than 7 years of age, it should almost always be used in a combined product with tetanus toxoid and pertussis vaccine. Poliomyelitis vaccine consisting of inactivated poliovirus may be included as a fourth antigen, but live, oral, poliovirus vaccine consisting of attenuated virus is currently preferred for poliomyelitis immunization in the United States. The triple antigen products are preferred over monovalent diphtheria toxoid not only because of efficiency and economy but also because pertussis vaccine enhances the immunogenicity of the toxoids (adjuvant effect). Also, the adsorbed products are more antigenic than the fluid products and the antitoxic immunity is of longer duration.

Thus, it is strongly recommended that routine immunization of children under 7 years of age against diphtheria be accomplished by the use of combined adsorbed diphtheria and tetanus toxoids and pertussis vaccine (DTP), according to schedules recommended by the Public Health Service Advisory Committee on Immunization Practices of the United States Public Health Service, the American Academy of Pediatrics, and th American Public Health Association. These advisory bodies also rec- ommended the use of adsorbed combined tetanus and diphtheria toxoids of the adult type (Td) for primary immunization of children older than 6 years and adults. However, the efficacy of Td as a primary immunizing agent against diphtheria has not been firmly established. (See Special Problems, Number 1, diphtheria toxoid generic statement.)

In the unusual instances in which primary immunization with mono- valent diphtheria toxoid is indicated, the adsorbed form is preferable. Primary immunization with adsorbed toxoid comprises three doses, 2 given 4 to 8 weeks apart, and the third dose (reinforcing) 1 year later. Booster doses should probably be given 5 years after the primar three doses and again after an interval of approximately 10 years. (Se Special Problems, Number 1, diphtheria toxoid generic statement.) In children older than 6 years and adults the booster doses should probabl be given as one-fifth of the usual dose or as Td because of an increase likelihood of reactions. Monovalent diphtheria toxoid may be used for booster doses in the presence of an outbreak of diphtheria, but usually under these circumstances advantage should be taken of the opportunity to enhance tetanus immunity by the use of Td.

If the fluid toxoid is used, primary immunization should include 4 doses, 3 doses 4 to 8 weeks apart, and a fourth dose 1 year later. Booster doses should be given as with the adsorbed preparation.

The fluid toxoid may be administered subcutaneously or intramuscularly. The adsorbed toxoid is preferably administered intramuscularly.

Absolute contraindications to the use of diphtheria toxoid are virtually nonexistent. Apparent anaphylactic reactions to diphtheria toxoid have been rarely reported. A marked febrile response to an injection should be cause for reducing the subsequent dose to one-tenth or one-fifth the former dose. Individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum immunologic response; accordingly, if discontinuation of such drugs is anticipated within the immediate future, immunization should be delayed until that time. In the presence of a febrile illness it is advisable not to administer diphtheria toxoid alone or in combination with pertussis vaccine because of possible confusion as to the cause of further fever.

Inasmuch as clinical diphtheria may not induce adequate active immunity, immunization of individuals who have recovered from diphtheria and who remain Schick-test positive should be undertaken employing a reduced initial dose because of possible sensitivity.

Safety

Fluid and adsorbed diphtheria toxoid must be tested to ensure sterility, the absence of free toxin, and the absence of blood group substances in significant amount. All of these tests are well defined

and described by the Bureau of Biologics. Experience with the administration of millions of doses has shown that life-threatening reactions to this toxoid are extremely rare. Transient local reactions and system: symptoms, primarily fever, are frequent, especially in individuals sensitized by prior exposure to the toxin or toxoid. These reactions are not life-endangering and usually persist only a day or two. The severity of these reactions is directly proportionate to the amount of toxoid administered.

Manufacturers are required to record all reported reactions.

Efficacy

Although controlled studies employing currently acceptable design methodology and statistical analysis have not been carried out, extensive experience in many countries has shown that the systematic use of this product for the immunization of infants and children has been associated with a striking reduction in the incidence of the disease. Similar but less extensive experience indicates comparable effectiveness in older age groups.

The potency of diphtheria toxoid prior to administration to humans is tested in guinea pigs, and standard procedures for such testing have been developed and are required of manufacturers by the Bureau of Biologics. In the case of the fluid toxoid, each lot must be tested by immunizing guinea pigs, followed by subsequent challenge with toxin to show protection. Unimmunized control animals must be employed to ensure the lethality of the toxin used to challenge the immunized animals.

Adsorbed diphtheria toxoid is tested by immunizing guinea pigs and subsequently determining diphtheria antitoxin levels as prescribed.

Quantitative correlation, however, between the results of animal protection tests and primary immunogenicity in man has not been established, although it is assumed that there is a direct relationship. For primary immunization, direct testing of antitoxin response in man should be required, and should be repeated whenever significant changes in the manufacturing process are made. However, past experience indicates that all toxoids which meet the requirements of the Office of Biologics Research and Review (OBRR) for potency in animals have proved effective as boosters in man. (See Special Problems, Number 3, Diphtheria Toxoid Generic Statement.)

Because field testing of disease prevention is currently not feasible, testing for efficacy in man requires evaluation of the induction of serologic immunity. This may be achieved by serological tests, or by the performance of the Schick skin test which reflects serologic and clinical immunity with satisfactory accuracy. Three doses of the fluid toxoid, given 4 weeks apart, or 2 doses of the adsorbed preparation, separated by 4 weeks, should result in at least 80 percent conversion of Schick positive or seronegative subjects to the Schick negative state or to seropositivity (0.01 or more units of diphtheria antitoxin per mL of serum) by 1 month after the last dose. To avoid confounding by anamnestic responses, use of the Schick test technique for efficacy testing in man should be limited to young infants clearly receiving primary immunization. Similarly, infants should be used for

serologic testing, or a blood sample should be drawn 7 days after the first dose and tested for evidence of an accelerated immune response which, if absent, would indicate primary immunization.

Special Problems

Diphtheria toxoid, as an immunizing agent in man, presents several problems that warrant efforts toward solution.

1. Although the safety of different lots of diphtheria toxoid products may be assured by animal testing, no animal model or other laboratory technique for evaluation of effectiveness has been directly correlated with primary immunogenicity in humans with acceptable precision. Titers of antibodies as determined by neutralization of the toxin in experimental animals or in tissue culture systems are better related to immunity than is the presence of hemagglutinating antibodies in serum specimens. However, the presence of low neutralizing titers does not ensure protection against large amounts of toxin.

2. The nonspecific reactogenicity of diphtheria toxoid, probably due largely to extraneous proteins derived from the organisms, represents a complicating factor in the immunization of individuals who have become sensitized to these proteins. The Panel has noted that there are no purity requirements in terms of Lf content per milligram of nitrogen except for the Td product.

3. For several reasons, diphtheria toxoid, fluid or adsorbed, is not as effective an immunizing agent as might be anticipated. First, clinical diphtheria may occur occasionally in immunized individuals-- even those whose immunization is reported as complete by recommended

regimens. However, when it does occur in such individuals, it appears to be milder. Second, diphtheria toxoid provides protection only against the toxin and not against the somatic components of Corynebacterium diphtheriae. Occasional local infections, respiratory or cutaneous, may occur in immune individuals and nontoxigenic strains may produce focal infections. Although both of these situations are encountered from time-to-time, they are not of major importance. Third, the permanence of immunity induced by the toxoid in the light of decreasing likelihood of exposure to the organism (the "streetcar booster") is open to question. In the absence of occasional exposure, it is possible that individuals immunized as children will not retain a degree of immunity that will provide adequate protection in later years. Fourth, the smaller amount of diphtheria toxoid present in tetanus and diphtheria toxoids combined for adult use (Td) has never been shown conclusively to be an adequate primary immunizing agent. Furthermore, the intervals between booster doses of Td in adults sufficient to maintain diphtheria immunity have not been established. Fifth, commendable efforts by producers to reduce the nonspecific reactivity of the toxoid by increased purification may have resulted in diminished immunogenicity.

Finally, the absence of proof recently obtained in humans for certain diphtheria toxoids by simple serological tests of readily measurable antibodies could not allow a Category I assignment. (See section 2.b. (2) of the Introduction in this Report.)

Recommendations

The following recommendations for the production, use, and evaluation of diphtheria toxoid are made:

1. Of maximum importance is the development of an animal or laboratory testing system that correlates consistently and with acceptable precision with primary immunogenicity in humans. Public funding to support such research should be made available. Until such a model is established, current toxoids and new variations on such toxoids will require field testing in humans employing serologic methods. Such field testing is expensive and difficult to conduct both because of the problem of finding suitable nonimmune subjects and because of the current restraints on research using human beings. Further, the necessity for field testing of each toxoid produced by a new or varied technique would understandably inhibit manufacturers in terms of innovation and improvement, and place a difficult burden upon the Bureau of Biologics in determining which alterations in production methods represent sufficient departures to warrant field testing. Enhanced correlation of existing animal models with immunogenicity in man would obviate such repetitive, time-consuming, logistically difficult, and expensive field studies.

2. Efforts should be made to reduce nonspecific reactogenicity of the toxoid. Standards should be established for purity of the toxoid in terms of Lf content per milligram of nitrogen.

3. Public support for the development of a more immunogenic toxoid should be considered. Of much lower priority is development of an

immunizing agent against components of the organism other than the toxoid.

Monitoring of the diphtheria immune status of the population by Schick testing or serologic testing would seem to be of maximum importance to prevent the development of a large population at risk in the future. The value of the Schick test is well established. However, the preparation of Schick test material is an understandably unprofitable undertaking for manufacturers. Public support may be necessary for continued production of this material, which is infrequently used but occasionally invaluable.
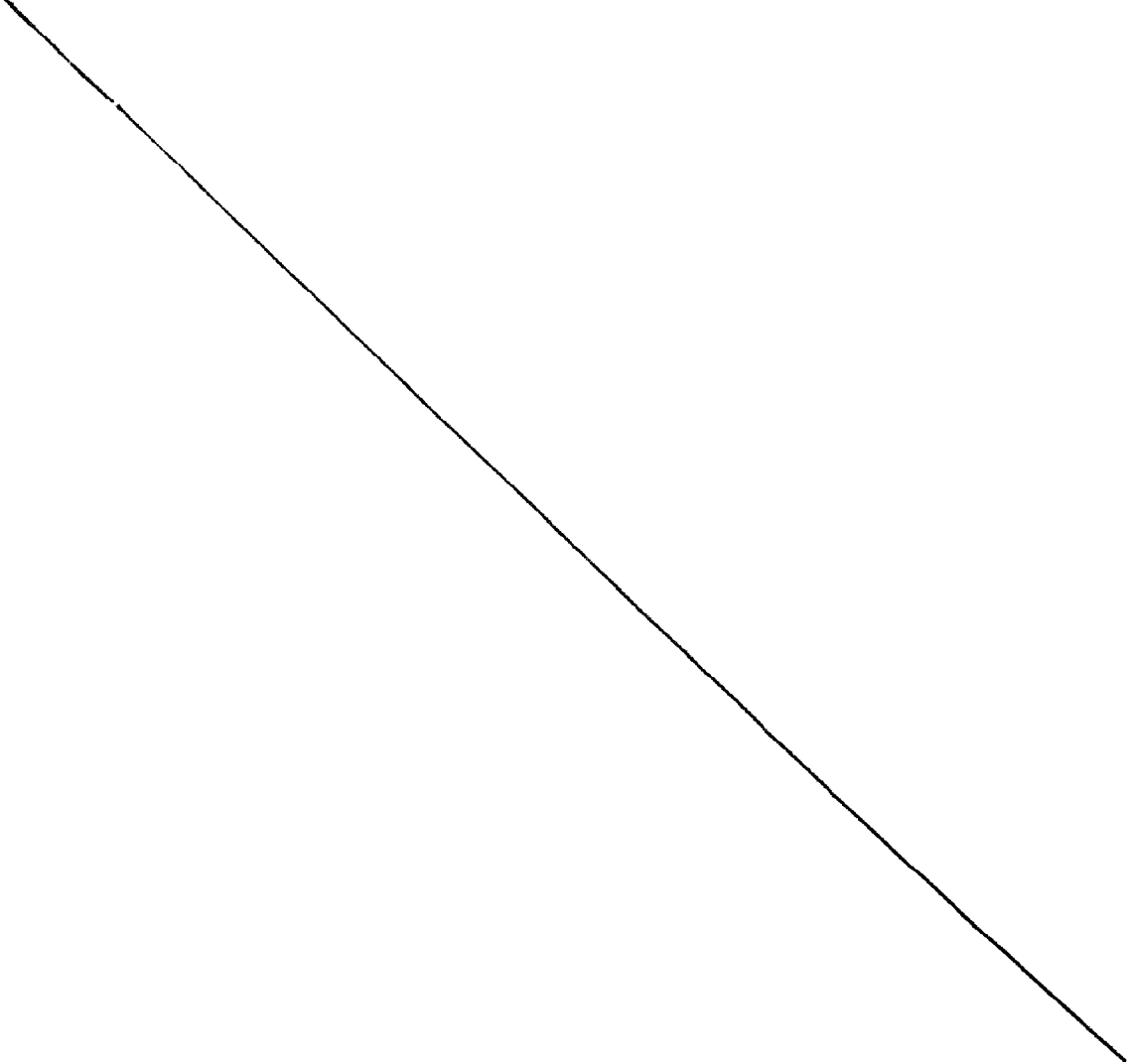
4. It is recommended that the apparent immunogenic superiority of the adsorbed toxoid over the fluid preparation be strongly emphasized and be included in labeling of products.

5. Finally, for the diphtheria toxoids whose effectiveness can be established by simple blood tests, there must be a resolution of the conflict in public policy between insistence on effectiveness data and constraints on obtaining such data resulting from the complex issue of informed consent. (See section 2.b. (2) in the Introduction to this Report.)

Basis for Classification

Past experience indicates that all diphtheria toxoids that meet the Bureau of Biologics' requirements for potency in animal tests have proved effective as boosters in man. Therefore, all currently licensed and marketed products are classified in Category I as regards their use for secondary or booster immunization.

However, quantitative correlation between primary immunogenicity in man and the results of animal protection tests has not been established; therefore direct testing of antitoxin responses in man is required, and should be repeated whenever significant changes in the manufacturing process are made. For these products, therefore, for which such evidence of effectiveness in primary immunization has not been acquired, Category IIIA is recommended.
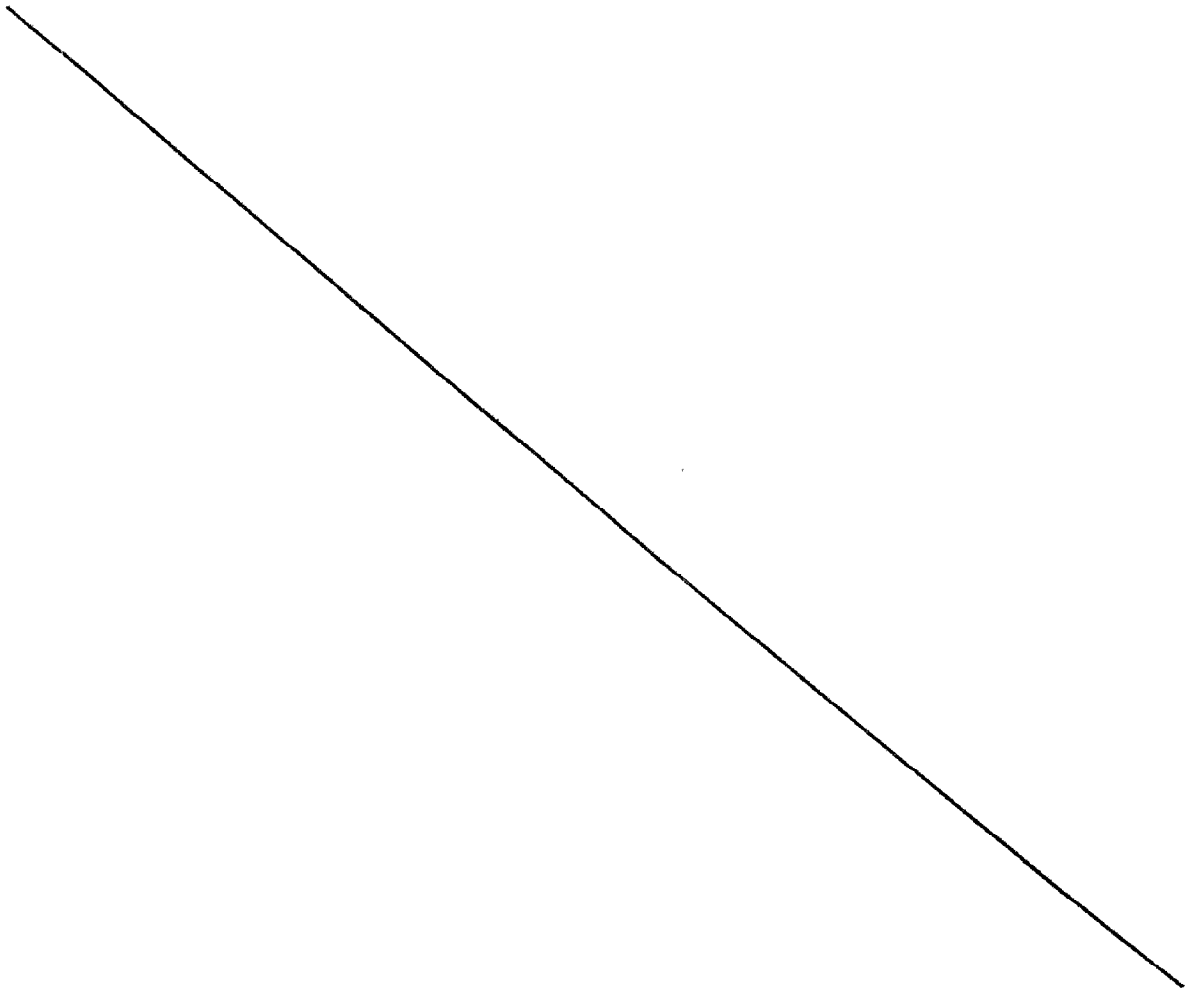
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(5) Center for Disease Control, "Reported Morbidity and Mortality in the United States, 1976," Morbidity and Mortality Weekly Report, Suppl., Health, Education, and Welfare Publication Number (Center for Disease Control) 77-8244, August 1977.

(6) "Diphtheria--Tetanus--Pertussis," in "Center for Disease Control, United States Immunization Survey: 1975," Health, Education, and Welfare Publication Number (Center for Disease Control) 76-8221, pp. 25-30, 1977.

(7) Miller, L. W., J. J. Older, J. Drake, and S. Zimmerman, "Diphtheria Immunization. Effect upon Carriers and the Control of Outbreaks," American Journal of Diseases of Children, 123:197-199, 1972.
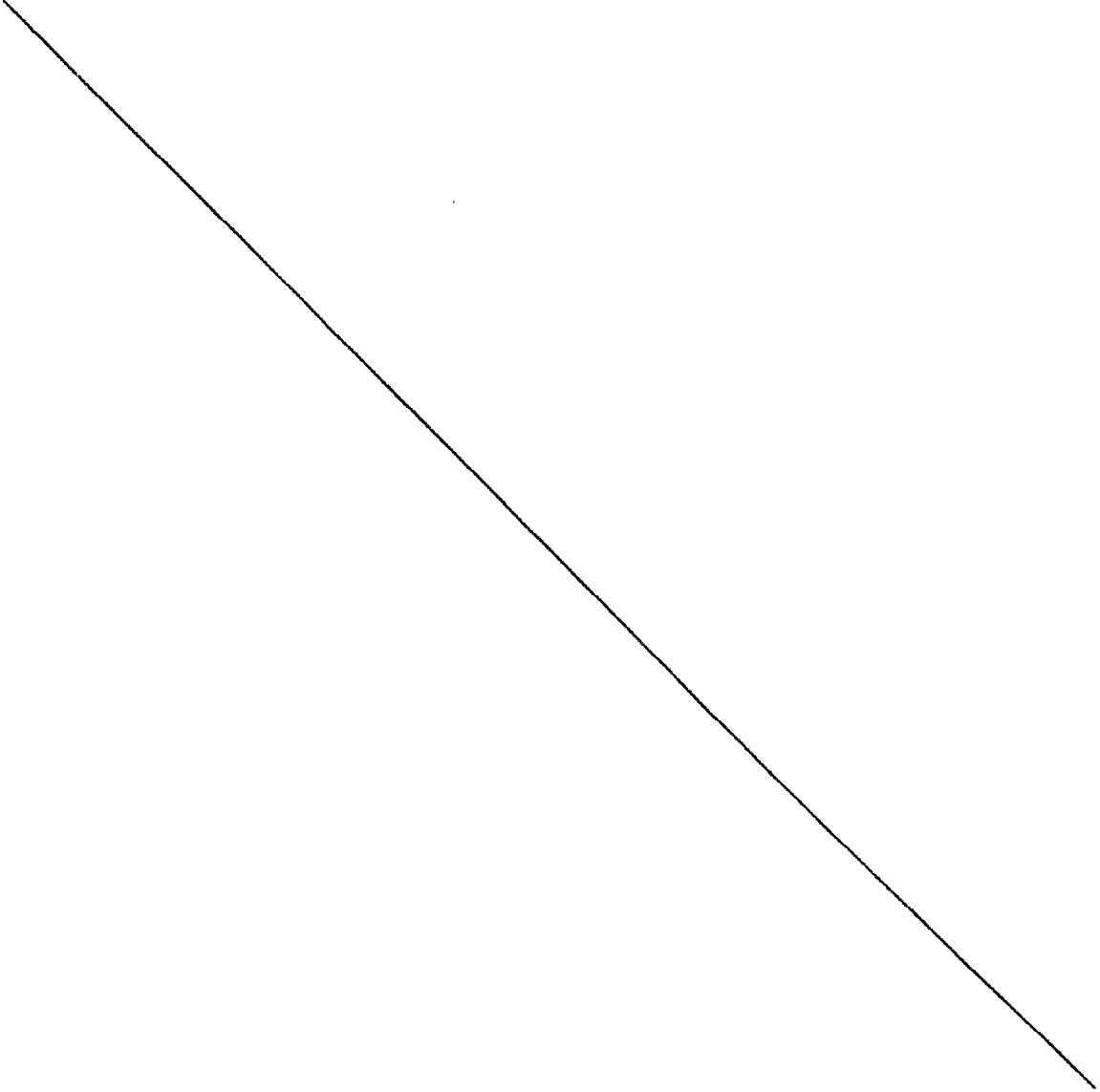
(8) Edsall, G., J. S. Altman, and A. J. Gaspar, "Combined Tetanus--Diphtheria Immunization of Adults: Use of Small Doses of Diphtheria Toxoid," American Journal of Public Health, 44:1537-1545, 1954.

SPECIFIC PRODUCT REVIEWS

DIPHTHERIA TOXOID ADSORBED MANUFACTURED BY BUREAU OF LABORATORIES, MICHIGAN DEPARTMENT OF PUBLIC HEALTH

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA TOXOID MANUFACTURED BY CONNAUGHT LABORATORIES LIMITED

1. Description. This product contains 40 to 50 Lf fluid diphtheria toxoid per mL. According to a revision of manufacturing procedures in 1973, the current product should contain 50 Lf per mL.

2. Labeling--a. Recommended use/indications. This preparation is recommended for active immunizations against diphtheria. Three doses of 1 cc (50 Lf) each at intervals of 4 weeks, beginning at 3 to 6 months of age. Reinforcing doses of 1 cc are given 1 year after the primary series and 4 years later. At school age an additional reinforcing dose of 0.1 to 0.2 mL may be given without being preceded by a reaction test.

b. Contraindications. Contraindications are not well outlined. Reaction tests are recommended in older children (over 8 years) and adults.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal requirements.

(2) Human. In studies (Ref. 1) carried out in 1964 to 1965, 68 children, ages 7 to 15 years, were evaluated for their diphtheria anti-toxin levels after 3 injections of Connaught Laboratories DT - polio vaccine. Sera from 54 children had no preimmunization antibody, and were considered to be primary responders. Eighty-three percent had protective levels of diphtheria antibody 1 month after the third injection.

b. Safety--(1) Animal. This product meets Federal requirements.

(2) <u>Human</u>. No data relating specifically to this product are presented. The manufacturer states that adverse reactions have not been reported.

c. <u>Benefit/risk ratio</u>. The benefit-to-risk assessment of the product is satisfactory.

d. <u>Labeling</u>. There is some inconsistency in labeling in the submission as to exact Lf content. Contraindications should be listed.

4. <u>Critique</u>. This product meets United States standards for animal safety and potency and appears safe in humans. Serologic data show adequate antibody response. The package insert should mention contraindications, and it should be stated that the preferred product for immunizations of infants is a combination product (DTP).

5. <u>Recommendations</u>. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

DIPHTHERIA TOXOID, FLUID, MANUFACTURED BY
DOW CHEMICAL COMPANY

1. _Description_. This manufacturer maintains a license for fluid diphtheria toxoid, although it has apparently never marketed the product as a monovalent antigen, either in the fluid or adsorbed form. Instead, it is supplied in 2 adsorbed products, 1 in combination with tetanus toxoid and the other with tetanus toxoid and pertussis vaccine. Techniques for preparation of the toxoid for ultimate combination meet or exceed Federal requirements.

2. _Labeling_--a. _Recommended use/indications_. Nonexistent because the product is not marketed.

b. _Contraindications_. Nonexistent because the product is not marketed.

3. _Analysis_--a. _Efficacy_--(1) _Animal_. This product meets Federal requirements when tested after combination with tetanus toxoid and adsorption.

(2) _Human_. No data relating directly to this product are available.

b. _Safety_--(1) _Animal_. This product meets Federal requirements when tested after combination with tetanus toxoid and adsorption.
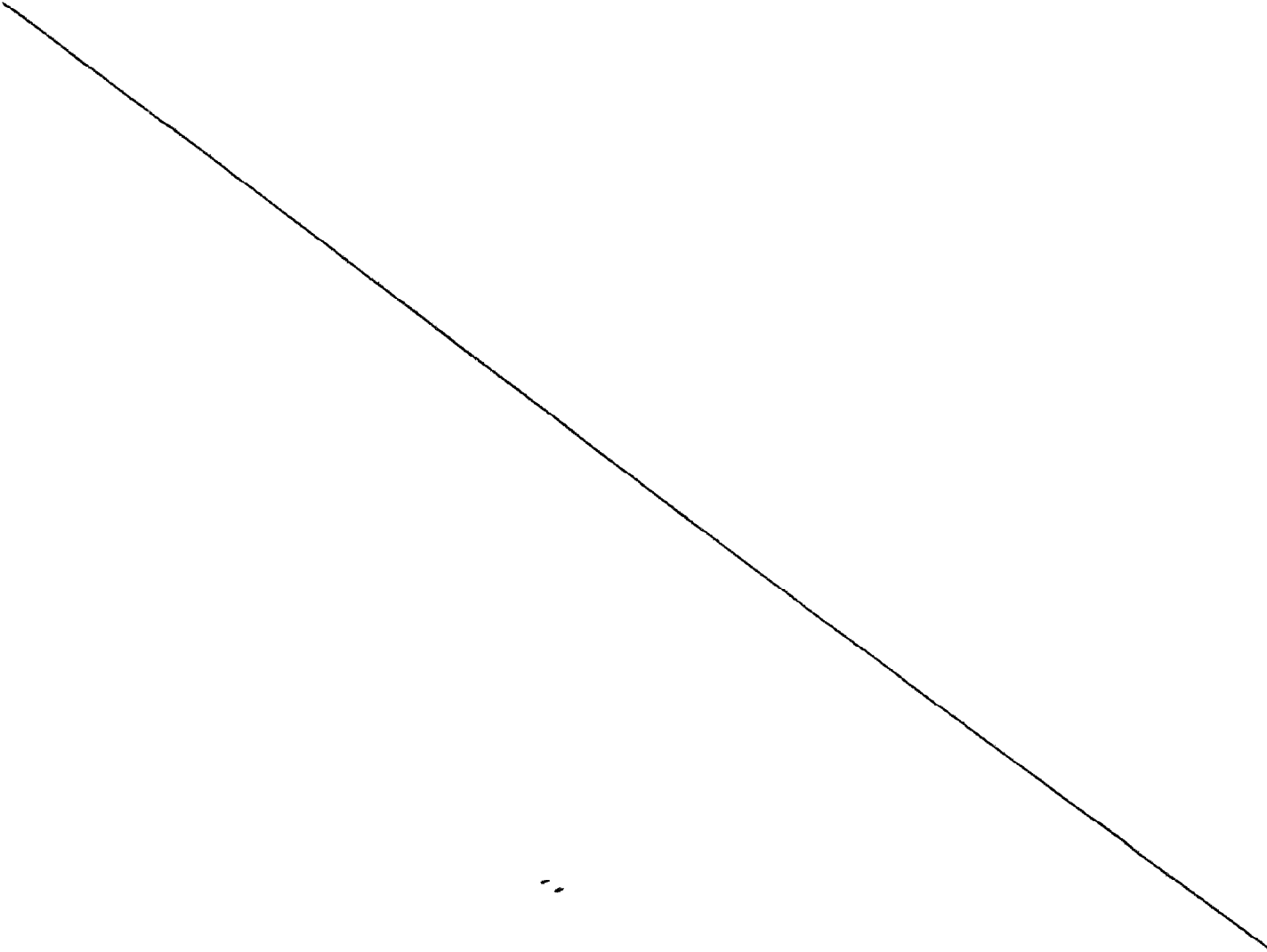
(2) _Human_. No data relating specifically to this product are available. There have been only 5 reports in a 10-year period of reactions to the adsorbed product combined with tetanus toxoid, and all 5 of these were insignificant.

c. <u>Benefit/risk ratio</u>. The benefit-to-risk assessment cannot be determined for this unmarketed product.

4. <u>Critique</u>. The manufacturer maintains a license for diphtheria toxoid, fluid, although it has never been marketed in the monovalent form. Inasmuch as the manufacturer does maintain a license for 2 combined forms of adsorbed diphtheria toxoid, the Panel believes that maintenance of this license is superfluous.
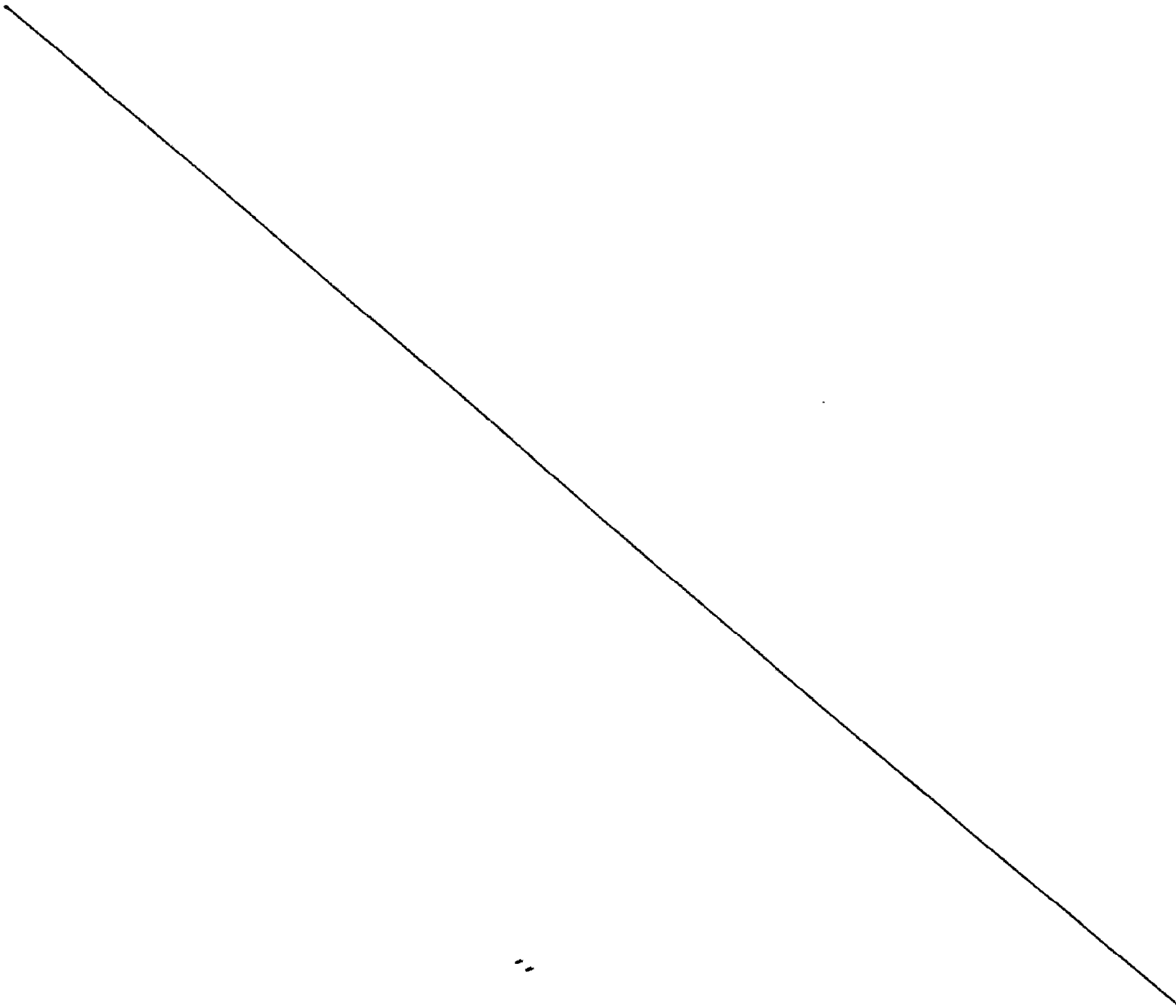
5. <u>Recommendations</u>. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA TOXOID MANUFACTURED BY ISTITUTO
SIEROTERAPICO VACCINOGENO TOSCANO "SCLAVO"

No data have been provided by the manufacturer for diphtheria toxoid, for which they are presently licensed. In the absence of any information from the manufacturer, the Panel can make no determination regarding the relative benefits and risks of this product.

Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked pending submission of evidence regarding the safety and effectiveness of this product.

DIPHTHERIA TOXOID ADSORBED MANUFACTURED BY ISTITUTO
SIEROTERAPICO VACCINOGENO TOSCANO "SCLAVO"

1. Description. A diphtheria toxoid purified by the metaphos-
phoric acid method, containing 15 Lf of toxoid per 0.5 mL dose, and 2 mg
aluminum hydroxide per 0.5 mL dose[1/] (80 percent of maximum permitted
amount). It is preserved in thimerosal at a concentration of 1:10,000.

2. Labeling--a. Recommended use/indications. For active immuni-
zation against diphtheria in children under 6, two 0.5 mL doses 6 to 8
weeks apart and a "booster" dose 1 year later. There is no discussion
concerning choice of this product as against diphtheria toxoid or diph-
theria and tetanus toxoids and pertussis vaccine. The container label
should say "SHAKE WELL."

b. Contraindications. Acute or active infections and temporary
immunosuppression; in situations involving prolonged immunosuppression
an extra dose is recommended.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal
requirements.

(2) Human. A "controlled study" (Ref. 2) is cited using this
toxoid in combination with typhoid-paratyphoid A and B (TAB) for chil-
dren all previously immunized against diphtheria. Three to 4-fold
increases in antitoxin titer were observed. Additional data submitted
on DT and Td provided evidence of effectiveness.

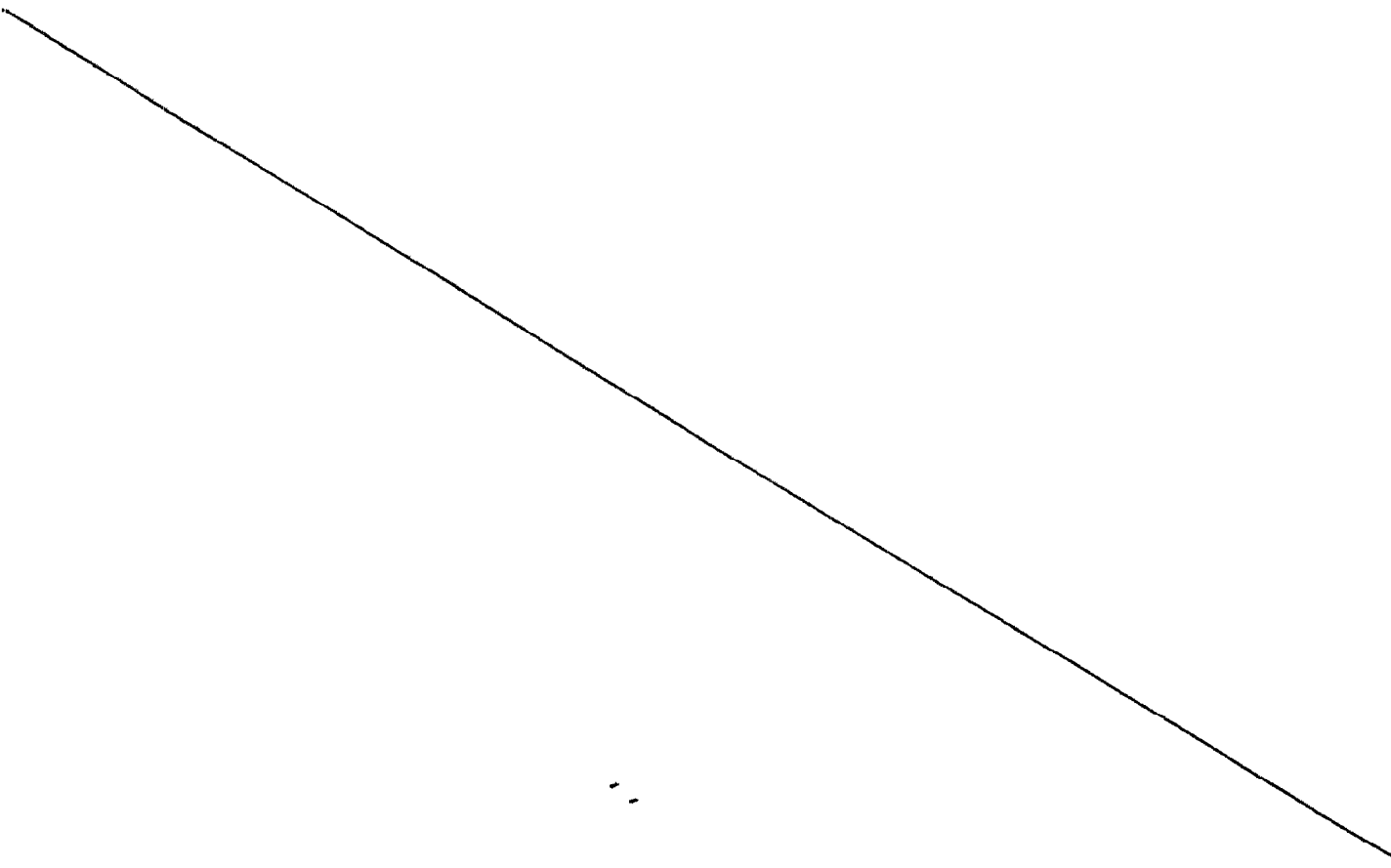b. Safety--(1) Animal. This product meets Federal requirements.

[1/]The label submitted to the Panel is wrong. This product contains 1
of $Al(OH)_3$ per dose. It is the Panel's understanding that the labeling
has been corrected.

(2) <u>Human</u>. The lack of complaints or claims against the product suggest that it is presumably not unduly reactive.

4. <u>Benefit/risk ratio</u>. The benefit-to-risk assessment of this product is satisfactory.

5. <u>Critique</u>. Additional data were provided to the Panel subsequent to the original submission. The data were submitted as part of a license application to FDA for DT and Td products, but in accordance with the guidelines established by the Panel regarding the extrapolation of data from the use of combined vaccines, there was sufficient information to show that this product is safe and effective.

6. <u>Recommendations</u>. The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling should be revised in accordance with currently accepted guidelines and the recommendations of the Report.

DIPHTHERIA TOXOID MANUFACTURED BY MASSACHUSETTS PUBLIC HEALTH BIOLOGIC LABORATORIES

1. <u>Description</u>. This is a fluid diphtheria toxoid, which is no longer issued. It contains 20 Lf of diphtheria toxoid per mL. No information on production details is provided. The diluting medium is sodium chloride, buffered with 0.05 M phosphate buffer. The preservative is thimerosal in concentration 1:10,000.

2. <u>Labeling</u>--a. <u>Recommended use/indications</u>. No labeling is included in the submission.

b. <u>Contraindications</u>. No labeling.

3. <u>Analysis</u>--a. <u>Efficacy</u>--(1) <u>Animal</u>. This product meets Federal requirements.

(2) <u>Human</u>. Several published reports on the efficacy of the manufacturer's products are cited in the submission (Ref. 3). In the 1950's, this toxoid appeared efficacious in eliciting antitoxin response in persons who did not demonstrate measurable antitoxin in their blood.

b. <u>Safety</u>--(1) <u>Animal</u>. This product meets Federal requirements.
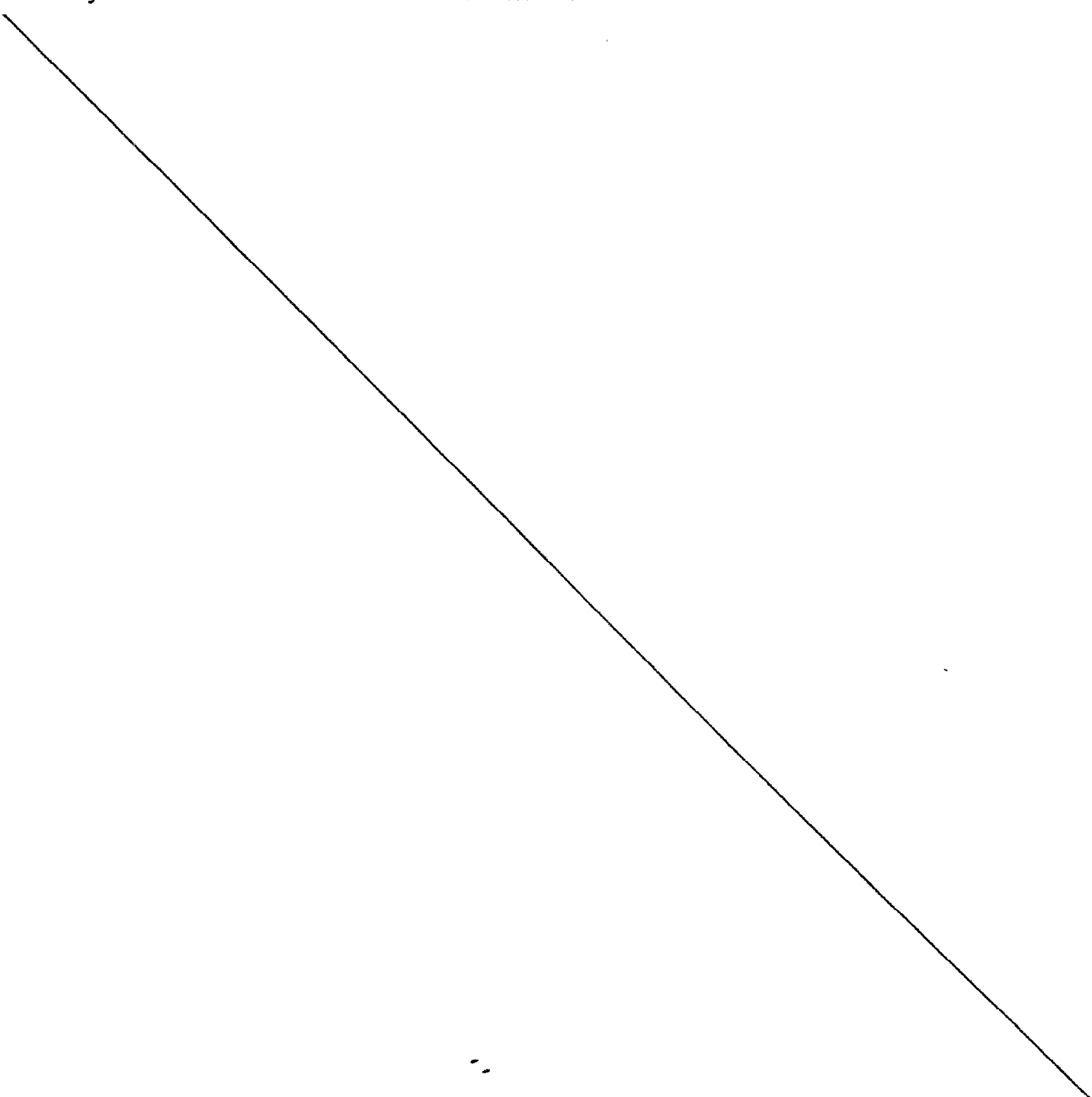
(2) <u>Human</u>. Safety data are presented (Ref. 3) from a multitude of publications from the 1950's and 1960's, and suggest that the product is innocuous.

c. <u>Benefit/risk ratio</u>. The benefit-to-risk assessment for this product appears to be satisfactory.

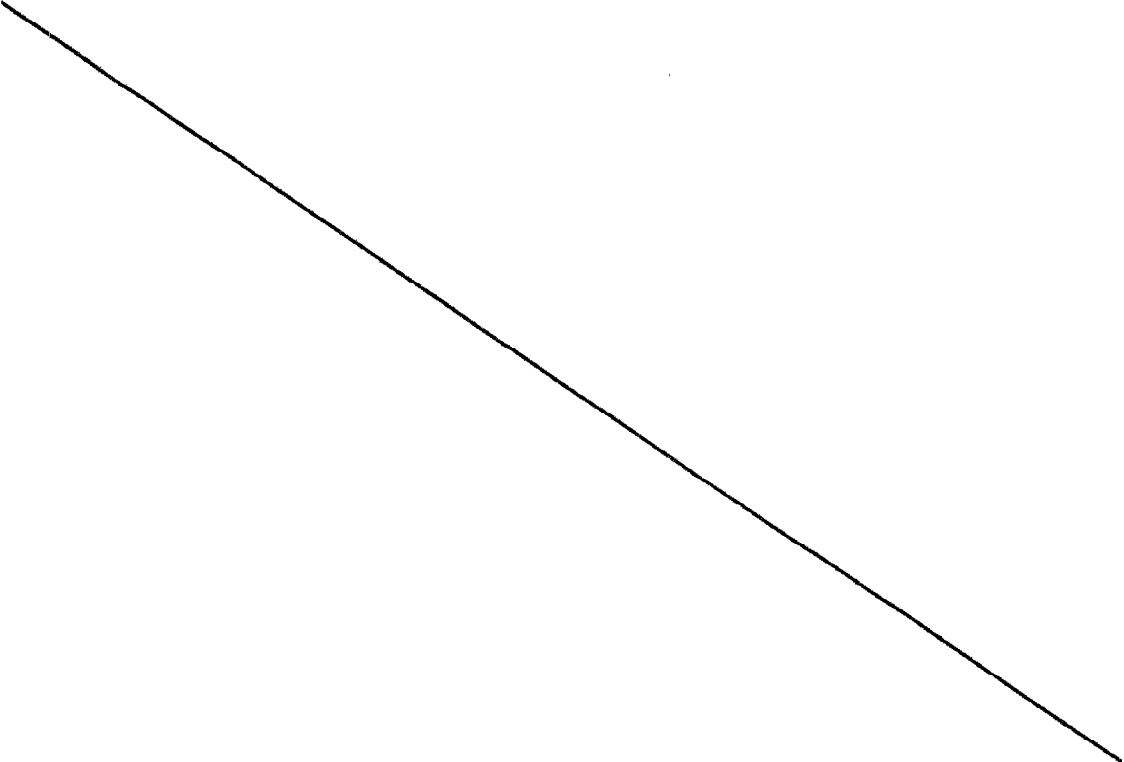4. <u>Critique</u>. This fluid diphtheria toxoid has been shown to be

safe, and the data from the literature support its efficacy when used as directed for primary immunization. No package insert is provided.

5. <u>Recommendations</u>. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in this country in the form for which licensed.

DIPHTHERIA TOXOID MANUFACTURED BY MERRELL-NATIONAL
LABORATORIES, DIVISION OF RICHARDSON-MERRELL INC.

Recommendations. The Panel recommends that this product be placed
in Category IIIC and that the appropriate license be revoked for admini-
strative reasons because this product is not marketed in the form for
which licensed and consequently there are insufficient data on labeling,
safety, and effectiveness.

DIPHTHERIA TOXOID, FLUID, MANUFACTURED BY
PARKE, DAVIS & COMPANY

1. Description. This is a fluid diphtheria toxoid containing 88 Lf of diphtheria toxoid per 0.5 mL dose. The final product contains 0.5 percent glycerin, 1:10,000 thimerosal as a preservative, and is suspended in isotonic sodium chloride. A strain of Corynebacterium diphtheriae PW8 of proven toxigenicity is used for toxin production. Formaldehyde is used as the toxoiding agent, and the toxoid is then further purified by ultrafiltration, ammonium sulfate precipitation, and subsequent dialysis.

This product is not currently on the market, but the manufacturer wishes to retain its license for possible future public health and medical demand.

2. Labeling--a. Recommended use/indications. No labeling was submitted.

b. Contraindications. No labeling was submitted.

3. Analysis--a. Efficacy--(1) Animal. This product meets Federal minimum requirements for diphtheria toxoid.

(2) Human. In 1961 to 1962, as part of a combined evaluation of diphtheria and tetanus toxoids, and poliomyelitis vaccine, a total of 61 prison inmates were given a variety of preparations containing Parke-Davis diphtheria toxoid singly or in combination with tetanus toxoid and poliomyelitis vaccine (Ref. 4). In most instances the doses administered probably elicited booster responses. It is not stated, however,

whether the products used were fluid or adsorbed toxoids. Furthermore, it was not clear whether the vaccines were experimental lots or the toxoids currently in use.

b. Safety--(1) Animal. This product meets Federal requirements for diphtheria toxoid.

(2) Human. No data were provided to substantiate the safety of this product.

c. Benefit/risk ratio. This cannot be determined in the absence of adequate data with regard to safety and efficacy.

4. Critique. This is a fluid diphtheria toxoid, currently licensed, but not marketed, which appears to meet animal efficacy and safety requirements. Satisfactory data have not been provided by which to assess either the safety or efficacy of this product in humans, whether used for primary or booster immunization.

No labeling has been submitted.

The Panel has a general concern about the present indications for the use of fluid diphtheria toxoid, in view of the greater and more durable immunity provided by adsorbed toxoids.

5. Recommendations. The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

DIPHTHERIA TOXOID ADSORBED MANUFACTURED BY
PARKE, DAVIS & COMPANY

1. Description. This is an aluminum phosphate adsorbed diphtheria toxoid, containing 15 Lf per 0.5 mL dose, and 2.5 mg of aluminum phosphate per 0.5 mL dose. It is suspended in 0.9 percent saline, and 1:10,000 thimerosal is included as a preservative. The manufacturing process, clarified in a supplemental submission, defines the strain of Corynebacterium diphtheriae to be used, and outlines a process of ultrafiltration, ammonium sulfate precipitation, and subsequent dialysis. This product is not currently on the market, but the manufacturer wishes to retain its license for possible future public health and medical demand.

2. Labeling--a. Recommended use/indications. This product is said to be recommended for the active immunization of children from 6 months to 8 years of age, where a multiple antigen is not indicated. The labeling further states that this product may be used to immunize older children and adults, but with appropriate caution because of the possibility of reactions.

A complete immunizing treatment is said to consist of two 0.5 mL doses at intervals of 4 to 6 weeks. A recall dose 1 to 2 years after the initial course is recommended for full protection. The labeling was last revised in December 1964, and thus differs strikingly from current national recommendations.

b. Contraindications. No absolute contraindications are listed. Children with a negative Schick test are recommended not to receive diphtheria toxoid.

ANTHRAX VACCINE ADSORBED (BIOTHRAX™)

DESCRIPTION

Anthrax Vaccine Adsorbed, (BioThrax™) is a sterile, milky-white suspension (when mixed) made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *Bacillus anthracis*. The production cultures are grown in a chemically defined protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts and sugars. The final product, prepared from the sterile filtrate culture fluid contains proteins, including the 83kDa protective antigen protein, released during the growth period. The final product contains no dead or live bacteria. The final product is formulated to contain 1.2 mg/mL aluminum, added as aluminum hydroxide in 0.85% sodium chloride. The product is formulated to contain 25 µg/mL benzethonium chloride and 100 µg/mL formaldehyde, added as preservatives.

CLINICAL PHARMACOLOGY
Epidemiology

Anthrax occurs globally and is most common in agricultural regions with inadequate control programs for anthrax in livestock. Anthrax is a zoonotic disease caused by the Gram-positive, spore-forming bacterium *Bacillus anthracis*. The spore form of *Bacillus anthracis* is the predominant phase of the bacterium in the environment and it is largely through the uptake of spores that anthrax disease is contracted. Spore forms are markedly resistant to heat, cold, pH, desiccation, chemicals and irradiation. Following germination at the site of infection, the bacilli can also enter the blood and lead to septicemia. Antibiotics are effective against the germinated form of *Bacillus anthracis*, but are not effective against the spore form of the organism.

The disease occurs most commonly in wild and domestic animals, primarily cattle, sheep, goats and other herbivores. In humans, anthrax disease can result from contact with animal hides, leather or hair products from contaminated animals, or from other exposures to *Bacillus anthracis* spores. It occurs in three forms depending upon the route of infection: cutaneous anthrax, gastrointestinal anthrax and inhalation anthrax.

Cutaneous anthrax is the most commonly reported form in humans (> 95% of all anthrax cases). It can occur when the bacterium enters a cut or abrasion on the skin, such as when handling contaminated meat, wool, hides, leather or hair products from infected animals or other contaminated materials. The symptoms of cutaneous anthrax begin with an itchy reddish-brown papule on exposed skin surfaces and may appear approximately 1-12 days after contact. The lesion soon develops a small vesicle. Secondary vesicles are sometimes seen. Later the vesicle ruptures and leaves a painless ulcer that typically develops a blackened eschar with surrounding swollen tissue. There are often associated systemic symptoms such as swollen glands, fever, myalgia, malaise, vomiting and headache. The case fatality rate for cutaneous anthrax is estimated to be 20% without antibiotic treatment.

Gastrointestinal anthrax usually begins 1-7 days after ingestion of meat contaminated with anthrax spores. There is acute inflammation of the intestinal tract with nausea, loss of appetite, vomiting and fever followed by abdominal pain, vomiting of blood and bloody diarrhea. There can also be involvement of the pharynx with sore throat, dysphagia, fever, lesions at the base of the tongue or tonsils and regional lymphadenopathy. The case fatality rate is unknown but estimated to be 25% to 60%.

Inhalation (pulmonary) anthrax has been reported to occur from 1-43 days after exposure to aerosolized spores.[1] Studies in rhesus monkeys indicate that a small number of inhaled spores may remain viable for at least 100 days following exposure.[2] However, information on how long spores remain viable in the lungs of humans is unavailable and the incubation period for inhalation anthrax is unknown. Initial symptoms are non-specific and may include sore throat, mild fever, myalgia, coughing and chest discomfort lasting up to a few days. The second stage develops abruptly with

findings such as sudden onset of fever, acute respiratory distress with pulmonary edema and pleural effusion followed by cyanosis, shock and coma. Meningitis is common. The fatality rate for inhalation anthrax in the U.S. is estimated to be approximately 45% to 90%. From 1900 to October 2001, there were 18 identified cases of inhalation anthrax in the U.S., the latest of which was reported in 1976, with an 89% (16/18) mortality rate. Most of these exposures occurred in industrial settings, i.e., textile mills.[3] From October 4, 2001, to December 5, 2001, a total of 11 cases of inhalation anthrax linked to intentional dissemination of Bacillus anthracis spores were identified in the U.S. Five of these cases were fatal.[4]

Mechanism of Action
Virulence components of Bacillus anthracis include an antiphagocytic polypeptide capsule and three proteins known as protective antigen (PA), lethal factor (LF) and edema factor (EF). Individually these proteins are not cytotoxic but the combination of PA with LF or EF results in the formation of the cytotoxic lethal toxin and edema toxin, respectively. Although an immune correlate of protection is unknown, antibodies raised against PA may contribute to protection by neutralizing the activities of these toxins.[5] The contribution of Bacillus anthracis proteins other than PA, that may be present in BioThrax, to the protection against anthrax has not been determined.

CLINICAL STUDIES
A controlled field study using an earlier version of a protective antigen–based anthrax vaccine, developed in the 1950's, that consisted of an aluminum potassium sulfate-precipitated cell free filtrate from an aerobic culture, was conducted from 1955-1959. This study included 1,249 workers [379 received anthrax vaccine, 414 received placebo, 116 received incomplete inoculations (with either vaccine or placebo) and 340 were in the observational group (no treatment)] in four mills in the northeastern United States that processed imported animal hides.[6] During the trial, 26 cases of anthrax were reported across the four mills - five inhalation and 21 cutaneous. Prior to vaccination, the yearly average number of human anthrax cases was 1.2 cases per 100 employees in these mills. Of the five inhalation cases (four of which were fatal), two received placebo and three were in the observational group. Of the 21 cutaneous cases, 15 received placebo, three were in the observational group, and three received anthrax vaccine. Of those three cases in the vaccine group, one case occurred just prior to administration of the scheduled third dose, one case occurred 13 months after an individual received the third of the scheduled 6 doses (but no subsequent doses), and one case occurred prior to receiving the scheduled fourth dose of vaccine. In a comparison of anthrax cases between the placebo and vaccine groups, including only those who were completely vaccinated, the calculated vaccine efficacy level against all reported cases of anthrax combined was 92.5% (lower 95% CI = 65%).

From 1962 to 1974, based on information reported to Centers for Disease Control and Prevention (CDC), 27 cases of anthrax occurred in mill workers or those living near mills in the United States. Of those, 24 cases occurred in unvaccinated individuals, one case occurred after the person had been given one dose of anthrax vaccine and two cases occurred after individuals had been given two doses of anthrax vaccine. No documented cases of anthrax were reported for individuals who had received the recommended six doses of anthrax vaccine. These individuals received either an earlier version of a protective antigen-based anthrax vaccine or BioThrax.

In an open-label safety study conducted by the CDC, BioThrax was administered in 0.5 mL doses according to a 0, 2, 4 week initial dose schedule followed by additional doses at 6, 12 and 18 months to complete the 6 dose vaccination series. Annual boosters were administered thereafter. In this study, 15,907 doses of BioThrax were administered to approximately 7,000 textile employees, laboratory workers and other at risk individuals and the incidence rates of local and systemic adverse reactions were recorded. (See ADVERSE REACTIONS)

A randomized clinical study was conducted by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) from 1996-1999 in 173 volunteers to evaluate changes to the vaccination